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HEI Public Health and Air Pollution in Asia Program

Part 4

Includes Commentaries by the Institute's Health Review Committee

Part 4

Interaction Between Air Pollution and Respiratory Viruses: Time-Series Study of Daily Mortality and Hospital Admissions in Hong Kong

Chit-Ming Wong, Thuan Quoc Thach, Patsy Yuen Kwan Chau, Eric King Pan Chan, Roger Yat-Nork Chung, Chun-Quan Ou, Lin Yang, Joseph Sriyal Malik Peiris, Graham Neil Thomas, Tai-Hing Lam, Tze-Wai Wong, Anthony Johnson Hedley

with a Commentary by the HEI Health Review Committee

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ABSTRACT

BACKGROUND

Populations in Asia are not only at risk of harm to their health through environmental degradation as a result of worsening pollution problems but also constantly threatened by recurring and emerging influenza epidemics and pandemics. Situated in the area with the world's fastest growing economy and close to hypothetical epicenters of influenza transmission, Hong Kong offers a special opportunity for testing environmental management and public health surveillance in the region.

In the Public Health and Air Pollution in Asia (PAPA*) project, the Hong Kong research team assessed the health effects of air pollution and influenza as well as the interaction between them. The team also assessed disparities in the health effects of air pollution between relatively deprived and more affluent areas in Hong Kong. The aim was to provide answers to outstanding research questions relating to the short-term effects of air pollution on mortality and hospital admissions; the health effects of influenza with a view to validating different measures of influenza activity according to virologic data; the confounding effects of influenza on estimates of the health effects of air pollution; the modifying effects of influenza on the health effects of air pollution; and the modifying effects of neighborhood social deprivation on the health effects of air pollution.

DATA

Data on mortality and hospital admissions for all natural causes, as well as the subcategories of cardiovascular diseases (CVD) and respiratory diseases (RD), were derived from the Hong Kong Census and Statistics Department and the Hospital Authority. Daily concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}), and ozone (O_3) were derived from eight monitoring stations with hourly data that were at least 75% complete during the study period.

Three measures of influenza and respiratory syncytial virus (RSV) activity were derived from positive isolates of specimens in the virology laboratory of Queen Mary Hospital (QMH), the main clinical teaching center at The University of Hong Kong and part of the Hong Kong Hospital Authority network of teaching hospitals: *influenza intensity* (defined as the weekly proportion of positive isolates of influenza in the total number of specimens received for diagnostic tests); the presence of *influenza epidemic* (defined as a period when the weekly frequency of these positive isolates is $\geq 4\%$ of the annual total number of positive isolates [i.e., twice the expected mean value] in two or more consecutive weeks); and *influenza predominance* (defined as a period of influenza epidemic when the weekly frequency of RSV was less than 2% for two or more consecutive weeks). The weekly proportion of positive isolates of

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The PAPA Program was initiated by the Health Effects Institute in part to support the Clean Air Initiative for Asian Cities (CAI-Asia), a partnership of the Asian Development Bank and the World Bank to inform regional decisions about improving air quality in Asia. Additional funding was obtained from the U.S. Agency for International Development and the William and Flora Hewlett Foundation. The contents of this document have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties and no endorsement by them should be inferred.

*A list of abbreviations and other terms appears at the end of the Investigators' Report.

RSV in total specimens was determined in the same way as for influenza intensity.

A social deprivation index (SDI) was defined by taking the average of the proportions of households or persons with the following six characteristics in each geographic area using the census statistics: unemployment; household income < U.S. $250 per month; no schooling at all; never-married status; one-person household; and subtenancy.

A Poisson regression with quasi-likelihood to account for overdispersion was used to develop core models for daily health outcomes, with a natural spline smoothing function to filter out seasonal patterns and long-term trends in this time-series study of daily mortality and hospital admissions, and with adjustment for days of the week, temperature, and relative humidity (RH). Air pollutant concentration values were entered into the core model to assess the health effects of specific pollutants. The possible confounding effects of influenza were assessed by observing changes in magnitude of the effect estimate when each influenza measurement was entered into the model; and interactions between air pollution and influenza were assessed by entering the terms for the product of the air pollutant concentration and a measurement of influenza activity into the model. A Poisson regression analysis was performed to assess the effects of air pollution in each area belonging to low, middle, or high social deprivation strata according to the tertiles of the SDI. The differences in air pollution effects were tested by a case-only approach.

RESULTS

The excess risk (ER) estimates for the short-term effects of air pollution on mortality and hospitalization for broad categories of disease were greater in those 65 years and older than in the all-ages group and were consistent with other studies. The biggest health impacts were seen at the extremes of the age range. The three measures employed for influenza activity based on virologic data — one based on a proportion and the other two using frequencies of positive influenza isolates — were found to produce consistent health impact estimates, in terms of statistical significance. In general, we found that adjustment for influenza activity in air pollution health effect estimations took account of relatively small confounding effects. However, we conclude that it is worthwhile to make the adjustment in a sensitivity analysis and to obtain the best possible range of effect estimates from the data, especially for respiratory hospitalization.

Interestingly, interaction effects were found between influenza activity and air pollution in the estimated risks for hospitalization for RD, particularly for O_3. These results could be explained in terms of the detrimental effects of both influenza viruses and air pollutants, which may be synergistic or competing with each other, though the mechanism is still unknown. The results deserve further study and the attention of both public health policy makers and virologists in considering prevention strategies.

IMPLICATIONS

In Hong Kong, where air pollution may pose more of a health threat than in North American and Western European cities, the effects of air pollution also interact with influenza and with residence in socially deprived areas, potentially leading to additional harm.

Asian governments should be aware of the combined risks to the health of the population when considering environmental protection and management in the context of economic, urban, and infrastructure development. This is the first study in Asia to examine the interactions between air pollution, influenza, and social deprivation from an epidemiologic perspective. The biologic mechanisms are still unclear, and further research is needed.

INTRODUCTION

OVERVIEW

Owing to rapid economic development and increasing fossil fuel consumption, air pollution is now a major public health problem in the Asia-Pacific region. To date there have been several short-term health effects studies in Asia, but they may not be representative of all the different regions that may need government action to combat air pollution. In addition, the methodology of these individual studies may not be similar enough to allow joint assessment of the health effects relevant to Asia aimed at providing information for regional environmental policy decisions.

The PAPA project, of which this Hong Kong study is a part, was initiated to develop a common approach to the assessment of the short-term effects of air pollution in Asia. In particular, the project focuses on the estimation of the effects of air pollution on mortality in individual cities and makes comparisons between them. The cities studied include Bangkok, Thailand, and Hong Kong, Shanghai, and Wuhan, China, in the first wave, and then Delhi and Chennai, India, in the second wave.

Fast economic growth without proper environmental management strategy places countries in Asia at risk of serious harmful consequences from environmental degradation. Many sectors of the population in these regions are now facing widening disparities in the environment based on socioeconomic factors and, at the same time, experiencing

increasing hazards from the changing characteristics and epidemic potential of influenza viruses.

In this Hong Kong PAPA study, we investigated the short-term effects of air pollution and influenza on health outcomes and examined the role of influenza in the confounding and modifying of the health effects of air pollution. We also looked at the relationship between residence in a socially deprived area and the health effects of air pollution.

SHORT-TERM EFFECTS OF AIR POLLUTION

Air pollution is a global environmental problem, and the World Health Organization (WHO) has developed a series of reports to assess the relationship between air pollution and health (WHO 2003; WHO 2004a,b). Many health-impact assessments have demonstrated the adverse effects of air pollution, including particles and gases, on both mortality and hospital admissions. Samet and colleagues (2000a) demonstrated that an increase in the concentration of fine particulates was associated with an increase in mortality rates in 20 U.S. cities, and Sunyer and associates (2003) found an association between SO_2 and hospital admissions for CVD in 7 European cities. Evidence from different investigators in different populations at different times has shown that cardiopulmonary disease is the major disease category strongly associated with air pollution, with additional effects on maternal (Maisonet et al. 2004) and child (Gauderman et al. 2004) health.

There were more than 1000 individual studies with various study designs and 19 reviews identified when the terms "air pollution" and "health effects" were used to search the PubMed database in December 2006 for studies published from 1980 to June 2006. However, only 240 of these were from Asian cities, and most of those studies were from East Asia, including 16 (about 7%) from Hong Kong. Although the reported air pollution studies from Asia cover both mortality and hospital admissions, relatively few (only about 12%) of these studies used hospital admissions, visits, or discharges as the outcome measures (HEI 2006). In addition, the record from the U.S. studies is incomplete. In some of the U.S. studies (Krewski et al. 2000), the Medicare hospitalization database was used, which covers information only for people age 65 or older and the disabled, and does not represent the whole population. Some other countries represented in the literature do not possess computerized records of hospital admissions. As far as we know, there is no other study on both mortality and hospital admissions data available for the same study population in the same location covering the same period.

Hong Kong has the advantage of having electronic records of mortality data from a closely regulated and audited death registration system and from hospital admission/discharge databases, both of which are in the public sector. The Hong Kong government provides low-cost hospital services to the whole population, funded mainly by central government revenue with small copayments by patients, which are waived for the indigent (Leung et al. 2005). Public hospitals provide about 95% of the total hospital beds (Leung et al. 2005), while private hospitals cover the rest. Among all deaths, approximately 87% occur in public hospitals. Deaths occurring outside hospitals are usually subject to a coroner's inquest. This almost complete coverage of mortalities gives us adequate supporting information to estimate and interpret the risks of both hospital admissions and mortality in Hong Kong.

HEALTH IMPACT OF INFLUENZA

Influenza is an infectious disease that has a great impact on the health of populations worldwide and is associated with serious morbidity and mortality, especially in older people. However, the morbidity and mortality caused by influenza are often attributed to secondary bacterial infection, while the primary viral illness often goes unrecognized (Nicholson 1996). The impact of influenza on hospital admissions and mortality has long been recognized in temperate regions (Baltussen et al. 1998; Izurieta et al. 2000; Neuzil et al. 2000; Simonsen et al. 2000; Thompson et al. 2003, 2004), but only recently have studies in tropical and subtropical regions also demonstrated significant excess mortality and morbidity due to influenza in the general population (Wong CM et al. 2004, 2006; Chow et al. 2006; Li et al. 2006).

Hong Kong is close to the hypothetical epicenters of influenza pandemics originating in South China. It is situated in the latitude of the tropics and has a subtropical climate with four seasons. The annual mean temperature is 24℃, and the annual mean RH is 78%.

In temperate regions, there is a distinct seasonal peak in influenza activity, making the health impact of influenza easier to recognize than in tropical or subtropical regions. In particular, in temperate regions, where a single, distinct winter peak is observable, the difference in health outcome between *seasonal periods*, when virus circulation is high, and *baseline periods*, when influenza activity is low, can be used to assess health impact. Hong Kong usually has two influenza peaks, one in the cool season (January to March) and one in the warm season (July to August), but the pattern may vary from year to year. This varying pattern makes it more difficult to assess the health impact of influenza. Recently, we were able to show that influenza is a major cause of morbidity and mortality in the region (Wong CM et al. 2004, 2006).

The literature describes two ways to define influenza activity: one is based on the proportions of positive influenza isolates (Thompson et al. 2003; Wong CM et al. 2004, 2006; Chow et al. 2006) and the other, on the frequencies of positive influenza isolates for baseline, epidemic, and predominance periods (Izurieta et al. 2000; Chiu et al. 2002). Using the first definition, regression models developed for the assessment of daily time-series studies for the short-term effects of air pollution (Samet et al. 2000b, Wong CM et al. 2001, 2002; Samoli et al. 2006) have been applied in assessing the health impacts of influenza. Using the second definition of influenza activity, comparative approaches measuring the differences between a baseline and an influenza epidemic period, with or without taking into account the co-circulation of RSV, have been employed (Baltussen et al. 1998).

More reliable estimates of the role of influenza in determining health outcomes are important for informing global environmental health policy decisions, as highlighted in the "Adoption of Global Agenda on Influenza," published by WHO (WHO 2002). This is particularly true for tropical and subtropical regions where the possible health effects of influenza have not been studied thoroughly. Recently, regression methods have been used in combination with measures of influenza activities based on the proportion of positive influenza isolates derived from virology laboratories (Thompson et al. 2003; Wong CM et al. 2004, 2006; Chow et al. 2006). However, there remain issues regarding the validity of using the above-mentioned proportion as a measure of influenza activity.

CONFOUNDING EFFECTS OF INFLUENZA IN ESTIMATES OF HEALTH EFFECTS OF AIR POLLUTION

The association between the short-term effects of exposure to PM and mortality due to all natural and cardiovascular-related causes showed that the effects are not confounded by influenza epidemics (Braga et al. 2000; Touloumi et al. 2005). Touloumi and colleagues examined the confounding effect of influenza epidemics for PM_{10} in relation to mortality due to all natural and cardiovascular-related causes. They found that after adjustment for influenza epidemics, the effect estimates for PM_{10} ranged from 0.45% to 0.67% for mortality due to all natural causes and 0.86% to 1.06% for cardiovascular-related mortality for a 10-$\mu g/m^3$ increase in PM_{10} concentration for lags of 0 days (lag 0) and 1 day (lag 1). They concluded that influenza epidemics were unlikely to confound the associations between PM_{10} and mortality due to all natural and cardiovascular-related causes. In limited time-series studies describing the effect of air pollution, influenza epidemics were often controlled for by adding one dummy variable to the core model, usually based on retrospective non-virologic data of the 90th percentile of respiratory mortality distribution (Wong CM et al. 2001, 2002). However, this approach cannot account for possible heterogeneity in the effect of influenza itself. Touloumi and colleagues also suggested using a lag of about 1 week to identify the effects of influenza epidemics on mortality, but this limits the use of respiratory mortality to adequately adjust for confounding by influenza (Schwartz et al. 1996; Touloumi et al. 2005). These data suggest that the use of routine, weekly virologic data to control for influenza epidemics may be more appropriate. Gaseous pollutants were not considered in most of the studies describing potential confounding effects of influenza epidemics. We present in this study a formal assessment of confounding by influenza activity of the health effects related to all pollutants.

INTERACTION BETWEEN EFFECTS OF AIR POLLUTION AND INFLUENZA

We now know that influenza contributes to a heavy burden of morbidity and mortality for RD and CVD in Asia (Wong CM et al. 2004, 2006), as in the West. The effects of air pollutants and influenza viruses on disease pathogenesis may be synergistic since both factors affect the human host via the respiratory system — from the nasal cavity and nasopharynx to the main airways and alveoli — and also through systemic effects on the cardiovascular system. The transmission of influenza viruses is believed to be predominantly through short-distance dispersion of fine droplets. However, ambient air pollutants, especially PM_{10}, may facilitate the spread of influenza viruses by providing condensation nuclei for the virus droplets and may be critical to their long-range dispersion (Hammond et al. 1989).

Laboratory studies have provided much evidence to support an interaction between influenza and both gaseous and particulate air pollution in adversely affecting human health. As early as in the 1970s, a series of experiments in mice infected by influenza viruses showed an increased incidence of pneumonia after exposure to SO_2 (Fairchild et al. 1972). A more recent study showed that exposure to diesel exhaust, an important source of PM_{10}, could generate oxidative stress in human nasal and bronchial epithelial cells and also enhance the attachment of the influenza virus to these cells (Jaspers et al. 2005). Exposure to diesel exhaust during infection with influenza is also characterized by depression of interferon and hemagglutinin inhibitor levels in mice (Hahon et al. 1985).

Influenza has been considered a confounding factor in the assessment of the short-term effects of air pollution on human health in many multicity projects (Katsouyanni

et al. 2001; Touloumi et al. 2005). However, although there have been some attempts to discover the biologic mechanisms behind the interaction between air pollutants and influenza viruses (Fairchild et al. 1972; Jaspers et al. 2005), to date no epidemiologic study has explored the potential effect modification of influenza on the health effects of air pollution. A population-based study is required to determine whether there are interactions between influenza and air pollution.

HEALTH EFFECTS OF AIR POLLUTION IN SOCIALLY DEPRIVED AREAS

There is ample evidence that air pollution is a health hazard in both developed (Krewski et al. 2000) and developing (HEI International Scientific Oversight Committee 2004) countries. While all individuals are exposed to the risk of air pollution, those who are in poor health (Sunyer et al. 2000; Bateson and Schwartz 2004) or have a disadvantaged socioeconomic status (Jerrett et al. 2004; Neidell 2004; Forastiere et al. 2007) are affected most. Economic globalization has resulted in the shifting of notoriously polluted industries from wealthier to poorer regions where the costs of production are lower and environmental regulations are less stringent (Pulido 2000). Disparities in environmental health hazards among many countries have become greater. In local areas, particularly those with mixed residential and industrial activity, economically disadvantaged people have a higher risk of exposure to air pollution (Finkelstein et al. 2005). Because of this situation, governments have been urged to take social inequality into account when considering air quality interventions. Some studies in Europe and the United States have indicated a linkage between air pollution and poverty in terms of health impacts (Schwartz 2000; Zanobetti and Schwartz 2000; Filleul et al. 2004). However, we did not find any relevant study on this issue in the Asia-Pacific region. At the same time, air pollution is a growing environmental problem in Asian cities, leading to tremendous health problems and economic costs.

Oxidative stress and damage to the immune system, after both long- and short-term exposures, are the biologic mechanisms causing the adverse health effects of air pollution. In the current literature, there are two main hypotheses about possible interactions between the effects of air pollution and socioeconomic status on health. One hypothesis is that people in lower socioeconomic groups are more likely to live and work in places with higher levels of pollution so that their health may be compromised. The other hypothesis is that they are more likely to be disadvantaged socially and economically and are therefore more susceptible to the effects of air pollution than people with higher socioeconomic status (O'Neill et al. 2003). In this hypothesis, not only do socioeconomically disadvantaged people suffer more from poor health status because of their own personal factors and exposure, they are also subject to additional risks from air pollution.

Health effects associated with socioeconomic factors can be assessed at both the individual and neighborhood levels. Interactions between the effects of air pollution and socioeconomic status measured at the individual level have been demonstrated in several epidemiologic studies (Krewski et al. 2000, 2005; Filleul et al. 2004). However, interactions between air pollution and socioeconomic conditions measured at the neighborhood level have not been well studied, and the reported effects are still controversial (O'Neill et al. 2003). Whether or not residence in a socially deprived area subjects people to additional environmental health hazards is an important issue in public health, and appropriately designed research in this area is called for.

SPECIFIC AIMS

The aims of this study were to assess the following:

1. The short-term effects of air pollution on mortality and hospital admissions;
2. The health impact of influenza activity with a view to addressing the validity of three measures of influenza activity based on virologic data;
3. The confounding effects of influenza on the health effects of air pollution;
4. The interaction between the effects on health of air pollution and influenza activity; and
5. The interaction between the effects on health of air pollution and social deprivation at the neighborhood level.

METHODS AND STUDY DESIGN

DATA

All the data used in this study were derived from population, health service, and surveillance databases that employed routine collection. They included mortality data from the Hong Kong Census and Statistics Department, hospital admissions data from the city's Hospital Authority, air pollution data from the city's Environmental Protection Department, meteorologic data from the Hong Kong Observatory, and virologic data from the virology laboratory at QMH, as described in subsequent sections. Each database was scrutinized rigorously through quality

assurance and quality control reviews, and standard operating procedures (SOPs) for taking the measurements or for recording data were followed in the respective departments. In addition, all of our data collection methods and the data were assessed by the auditing team from the Health Effects Institute (HEI) (see Appendix R).

Mortality Data

The daily mortality data for the 7-year period from January 1996 to December 2002 were extracted from mortality records obtained from the Census and Statistics Department. The data included age, sex, date of death, place of residence (identified in terms of tertiary planning units [TPUs], a system devised by the Hong Kong Planning Department for town planning purposes), and underlying cause of death, coded according to the *International Classification of Disease, Revision 9* (ICD-9) in the years 1996–1999 and *Revision 10* (ICD-10) in the years 2000–2002 (see the Common Protocol at the end of this volume). Table 1 presents the causes of death by age group, along with the appropriate ICD-9 and ICD-10 codes for deaths considered in this study. All deaths of Hong Kong residents during this time period in these categories are represented.

Hospital Admissions Data

The hospital admissions data used in this study were based on the diagnoses of patients at discharge from January 1996 to December 2002. These diagnoses were obtained from the 19 acute and general hospitals of the Hospital Authority. The Hospital Authority manages more than 95% of hospital bed days in Hong Kong and maintains a central computerized clinical management system for entering and retrieving hospital stay information for all admitted patients. The hospital admissions data obtained for this study included the date of admission, sex, age, place of residence in terms of districts, and discharge diagnosis. Table 2 presents the discharge diagnoses considered in this study by age-specific groups, along with the appropriate ICD-9 code (the hospitals used only ICD-9 codes throughout the study period).

Air Pollutant and Meteorologic Data

The hourly pollutant data were provided and measured by the Environmental Protection Department from eight monitoring sites across Hong Kong (Appendix B). The monitoring stations were Central/Western (station 1), Kwai Chung (station 2), Kwun Tong (station 3), Sham Shui Po (station 4), Sha Tin (station 5), Tai Po (station 6), Tsuen Wan (station 7), and Yuen Long (station 8). NO_2, SO_2, PM_{10}, and O_3 were measured by chemiluminescence, fluorescence, tapered element oscillating microbalance (TEOM), and UV absorption, respectively. NO_2, SO_2, and O_3 were also measured by differential optical absorption spectroscopy in some monitoring stations. The equipment used for measurements, manufacturers, methods of measurement, and units is summarized in Appendix C.

Daily 24-hour average concentrations of NO_2, PM_{10}, and SO_2 and 8-hour maximum concentrations of O_3 were aggregated through hourly measurements. Data with fewer

Table 1. Causes of Death in the Mortality Data Considered for Analysis, by Age Group with ICD Code

Cause of Death	Age Group	ICD-9	ICD-10
All natural causes[a]	All ages, 0–4, 5–44, 45–64, 65+	001–799	A00–R99
Cardiopulmonary	All ages	390–459, 460–519	I00–I99, J00–J98
Cardiovascular	All ages	390–459	I00–I99
Cardiac or heart disease	All ages	390–398, 410–429	I00–I09, I20–I52
Stroke	All ages	430–438	I60–I69
Respiratory	All ages	460–519	J00–J98
LRI	All ages	466, 480–487	J10–J22
COPD	All ages	490–496	J40–J47
Accidental	All ages	800–999	S00–T98
Non-cardiopulmonary excluding accidental	All ages	001–389, 461–799	A00–H95, K00–R99

[a] All natural causes of death were defined as nonaccidental in this study.

Table 2. Discharge Diagnoses in Hospitalization Outcomes Data Considered for Analysis, by Age Group with ICD Code

Discharge Diagnosis[a]	Age Group	ICD-9
Cardiovascular	All ages, 0–14, 15–44, 45–64, 65+	390–459
Stroke	All ages	430–438
Ischemic heart disease	All ages	410–414
Respiratory	All ages, 0–14, 15–44, 45–64, 65+	460–519
Acute respiratory disease	All ages, 0–14	460–466, 480–487
Acute LRIs	All ages, 0–14	480–487
COPD	All ages, 65+	490–496
Asthma	All ages, 0–14	493

[a] Discharge diagnosis refers to the principal diagnosis listed on patients' medical records when discharged.

than 18 hourly measurements for NO_2, PM_{10}, and SO_2 and with fewer than 6 hourly measurements for O_3 per day between 10 a.m. and 6 p.m. were regarded as missing. O_3 measurements from station 3 were not included in this study, in accordance with this exclusion criterion.

Centering was done by subtraction of the mean concentration from the daily data of each station to avoid problems arising from differences in the levels of air pollutant concentrations among the eight monitoring stations (Wong CM et al. 2001). Daily mean pollutant concentration data for all of Hong Kong were derived by taking the arithmetic means of the data after centering over the eight monitoring sites. The daily mean temperature (degrees Celsius) and daily mean RH (%) were obtained from the Hong Kong Observatory.

Virologic Data

Weekly counts of positive isolates of influenza A and B viruses (*influenza A+B*) and RSV, as well as the total number of specimens tested, were obtained from the QMH virology laboratory in Hong Kong, which is part of the Department of Health (DH) surveillance network. This laboratory received an annual mean number of 6249 (range, 3098–8333) specimens for diagnosis of respiratory infections during the study period. The Virology Division of the DH surveillance network in Hong Kong also gathered virologic surveillance data, but it began its virology surveillance in 1998, two years later than the beginning of our study period, so we decided to use virologic data from QMH.

The specimens collected by QMH accounted for about 40% of the total specimens collected through the DH surveillance network for the whole territory of Hong Kong. We found that the virologic data from the DH and QMH laboratories were highly correlated ($r = 0.8$ for 1998–2002). Also, by means of a wavelet coherence analysis, which looked at whether the two time series oscillated simultaneously, we showed that the virologic data from the QMH were highly synchronized with data from the DH (data not shown). Owing to the compact geographic area of Hong Kong, these data should be representative of the influenza virus activity within the area under investigation.

We defined three measures of influenza activity using the virologic data to identify its association with mortality and morbidity:

1. *Influenza intensity*: The intensity of the influenza was defined by the weekly proportion of positive isolates of influenza A+B in the total number of specimens submitted for laboratory analysis. The measurement of the weekly proportions of influenza isolates has been widely adopted to assess the association between influenza and mortality and morbidity (Thompson et al. 2003, 2004; Wong CM et al. 2004) and was considered to provide better estimates than obtained when using other measure of influenza activity, particularly in subtropical and tropical regions (Wong CM et al. 2006). We used the weekly *proportion* of specimens positive for influenza virus instead of the *absolute numbers* of positive isolates to avoid potential bias caused by variations in the numbers of specimens collected in surveillance.
2. *Influenza epidemics*: We defined influenza epidemics as occurring when the weekly number of specimens positive for influenza A+B was $\geq 4\%$ of the annual total number of positive isolates for at least two consecutive weeks, as was also done in a previous Hong Kong study (Chiu et al. 2002). We defined the *epidemic baseline* to be when the weekly numbers of specimens positive for influenza were $< 2\%$ of the total annual

number for at least 2 consecutive weeks. We regarded other nonepidemic periods (i.e., when the weekly percentage was not < 4% for two or more weeks and also not at baseline) as *epidemic-intermediate.* This classification is relatively conservative; the baseline is higher than those adopted in other studies done in the temperate regions, which used the criterion of a weekly number of specimens positive for influenza being < 2% of the total annual positive numbers to define the baseline or nonepidemic period (Izurieta et al. 2000). We compared the influenza effect during epidemics with that during epidemic baseline periods.

3. *Influenza predominance*: RSV has been found to be a major cause of hospitalization in both children and the elderly, and exhibits clinical syndromes very similar to influenza (Nicholson 1996; Han et al. 1999; Zambon et al. 2001). To adjust for the cocirculation of RSV, we defined influenza predominance periods as those occurring when the weekly numbers of specimens positive for influenza were ≥ 4% and, *at the same time,* the weekly numbers of positive RSV isolates were < 2%, for at least 2 consecutive weeks. Correspondingly, the *predominance baseline* was defined as the period when the weekly numbers of specimens positive for influenza and for RSV were both < 2% for at least two consecutive weeks. Periods other than those considered to represent predominance or predominance baseline were defined as *predominant-intermediate*. We compared the influenza effect during influenza predominance with that during the predominance baseline periods.

All influenza measures were then converted into a daily format. Daily influenza intensity levels for a particular week were assumed to be the same for the whole week. For example, the influenza intensity level assigned to October 1, 1996, encompassed the weekly proportion of positive isolates of influenza A+B calculated for the week of September 29, 1996, to October 5, 1996. For influenza epidemics and predominance, dummy variables in each period were set up in a daily format to identify in which period a particular day should be included.

DATA QUALITY ASSURANCE AND QUALITY CONTROL

All of our databases were obtained through official government offices. Our team did not collect data directly but did review the quality assurance/quality control and SOP documentation for the data measurements and collection methods from each of the data sources. We also checked the values we received from the government offices against government reports to catch transcription errors.

Mortality Data

Appendix D is a flowchart, obtained from the DH, showing the registration procedure documenting causes of death for mortality statistics in Hong Kong. The underlying cause of death is determined through medical records and is entered into the medical certificate by the doctor who is certifying the death. The DH assigns the ICD code for the underlying cause of death and is responsible for ensuring the validity and accuracy of the codes. However, a formal analysis of the validity of the coding has not been documented.

We tabulated the annual number of deaths from our database and compared those numbers with the published statistical reports (Hong Kong Census and Statistics Department 2003). In one instance, we discovered that in some periods the percentage of missing data for date of death and area code was much greater than in other periods. We discussed this with officials in the Census and Statistics Department and found that there was a change in how the date of death was recorded at the end of year 1999. There were delays in reporting the dates of some deaths that had been undergoing coroner enquiries. We obtained the missing information on the dates of death and subsequently filled in most of the missing data, which resulted in only small proportions of missing data on date of death consistently occurring throughout the study period.

In addition, the codes for cause of death changed between 2000 and 2001 when the ICD-9 system was updated to ICD-10. However, we determined that the discrepancies were only in the coding of RD and that the number of death classifications affected was small and would not cause a major misclassification problem (Tsang and Cheung 2005).

Hospitalization Outcomes Data

The Hospital Authority's SOP for the collection of data has been published (Cheung et al. 2001a,b). We validated our data by tabulating the annual counts of different disease groups and comparing these counts with those in official reports.

Pollutant Data

The Hong Kong Environmental Protection Department has written SOP documentation and quality assurance/quality control procedures for each pollutant. Its system is accredited by the Hong Kong Laboratory Accreditation Scheme, which aims to maintain the standards of testing in and management of Hong Kong laboratories. We also compared the summary statistics obtained from our databases with the department's annual reports to ensure that there were no discrepancies arising between the databases (Hong Kong Environmental Protection Department 2002).

STATISTICAL METHODS AND DATA ANALYSIS

CORE MODEL DEVELOPMENT

For mortality outcomes, we used the statistical approach adopted by the PAPA teams and laid out in the Common Protocol (found at the end of this volume). We used generalized linear modeling to obtain adequate core models for each health outcome. We employed a Poisson regression using a quasi-likelihood method to model mortality and hospital admission counts with adjustment for overdispersion (McCullagh and Nelder 1989). To control for systematic variation over time, we introduced a "trend and seasonality" term and dummy variables for day of the week and public holidays. Other covariates considered and adjusted for were daily mean temperature and RH. The "trend and seasonality" term was defined by fitting either a natural smoothing spline or a penalized smoothing spline with 4 to 6 degrees of freedom (df) per year. Additional smoothing splines with 3 df to adjust for the effects of temperature and with 3 df to adjust for RH were included. The choice of the number of degrees of freedom for each smoothing function was made on the basis of observed residual autocorrelations using partial auto-correlation function (PACF) plots (see Figures E.1 and E.2 in Appendix E). A partial autocorrelation coefficient of $|\rho| < 0.1$ for the first two lag days was used as a criterion for a minimally adequate model. The randomness of residuals and auto-regressive terms were also considered in selecting the most appropriate models. The long-term trends in the residuals time-series plots show some patterns in small parts of the series. However, we are confident that most of the long-term variations have already been filtered out using 4 to 6 df per year, which are set a priori for the smoothing. Since our major objective was to assess the confounding and modifying effects of influenza, we did not adjust for influenza in the core model.

For hospitalization outcomes, since the daily variations of hospital admissions are greater than those of mortality, more degrees of freedom were needed in the spline smoothing functions of time trend, temperature, and RH. Moreover, since the preliminary results on mortality derived from natural splines and penalized splines were similar, only natural splines were used in the analysis of hospitalization outcomes.

First, we chose the appropriate degrees of freedom (range, 4–6 df per year) for the smooth function of time in order to achieve minimal autocorrelation of the residuals. We used a cross-validation criterion (specifically, CCV) to choose the appropriate degrees of freedom (range, 4–6 df per year) for the smooth function of time for the meteorologic terms. Afterward, we checked the analysis for model adequacy by looking at the residuals and PACF plots (see Figures F.1 and F.2 in Appendix F). When autocorrelation was present, model adequacy was improved by the addition of localized smoothing or the introduction of autoregressive terms. The degrees of freedom could also be increased beyond the predetermined limit of 6 to meet model adequacy criteria. We first attempted to increase the number of degrees of freedom in smoothing functions for the time trends within a range so that they would be comparable among the PAPA cities; but when this failed to produce adequate models as reflected in partial autocorrelations, we added autoregressive terms to the model to eliminate the serial correlation from the residuals (Brumback et al. 2000). This step was done after removing seasonal patterns and choosing the number of degrees of freedom for meteorologic factors.

ASSESSMENT OF MAIN, CONFOUNDING, AND INTERACTION EFFECTS OF AIR POLLUTION AND INFLUENZA

In this Hong Kong PAPA study, we assessed the main effects of air pollution and influenza, as well as the confounding and modifying effects of influenza on the effects of air pollution, with the influenza variables defined according to virologic data. After developing the finalized core model, we entered different variables of interest into the model to answer the research questions. The models were specified as follows:

- Model 1: Core model + air pollutant
- Model 2: Core model + influenza measures
- Model 3: Core model + air pollutant + influenza measures
- Model 4: Core model + air pollutant + influenza measures + air pollutant × influenza measures

Effects of Air Pollution Without Adjustment for Influenza: Model 1

To study the effects of air pollution on health outcomes, the concentrations of individual pollutants were added to the core model as linear terms. The ER from air pollution was reported for average concentrations for the average of a same-day and 1-day lag (lag 0–1 day). In calculating the ER, we first transformed the coefficient from the model into the relative risk per 10-μg/m^3 increase in concentration of pollutant. Then, we subtracted 1 from the relative risk and multiplied by 100 to convert the ER to a percentage. The following analyses were based on this predetermined lag 0–1 day. A nonsignificant result refers to a P value > 0.05.

Sensitivity analyses for the main effects of air pollution
The strategies for constructing a core model were developed a priori by the first four PAPA teams. These methods were adopted for the assessment of mortality effects, but were then modified slightly for the assessment of hospitalization outcome effects. We tried the following different strategies to check the robustness of the main effect estimates:

1. *Variations in the degrees of freedom*: To assess the robustness of the main effect estimates to variation in seasonality and time trend specified in the core model, we employed an alternative spline smoothing function for the time variable with 4 to 12 df.
2. *Lag effects*: We also examined the estimates at a single lag day from the current day (i.e., lag 0 day) up to lag 4 days and at an average concentration of lag 0 to lag 1 (lag 0–1) and lag 0 to lag 4 (lag 0–4) days in order to assess the patterns of the main effect estimates at various lag days.
3. *Confounding effects of temperature*: The confounding effects of temperature have been studied in short-term air pollution studies (Samet et al. 1998). We put an additional smoothing function for temperature, with an average of lag 1–2 days and 3–7 days, separately into the core model.
4. *Control causes of death*: In mortality analyses, we used accidental deaths and nonaccidental, noncardiopulmonary deaths as controls in cause of death.
5. *Concentration–response curves*: We produced concentration–response curves with a smoothing spline function for each pollutant at a fixed number of degrees of freedom (3 df). We also tested the deviance between models with pollutants represented as nonlinear terms and models with pollutants represented as linear terms.

Effects of Influenza: Model 2

To study the impact of influenza on health outcomes, three different influenza measures (influenza intensity, the presence of influenza epidemics, and influenza predominance) were added to the core model individually as linear terms, with adjustments for weekly proportions of positive isolates of RSV in the specimen total. For effect estimation by influenza intensity, the effects of the current week were fitted, and the effect estimates (specifically, the ER of a 10% change in influenza intensity) were reported. For estimates of effects on health outcomes by influenza epidemics, dummy variables for influenza epidemics and for the epidemic-intermediate period, defined according to virologic data, were added to the core model in order to assess the effect of influenza epidemics compared with the epidemic baseline. The ER of influenza epidemics compared with the epidemic baseline is reported here. For estimates of influenza activity on health outcomes using influenza predominance, dummy variables for influenza predominance and for the predominant-intermediate period were added to the core model in order to assess the effect of influenza predominance compared with the predominance baseline period, also reported here.

Air Pollution Effects with Adjustment for Influenza: Model 3

To study the effects of air pollution on health outcomes with adjustments for the effect of influenza and other respiratory viruses, Model 1, as defined earlier, was adjusted for weekly proportions of positive RSV isolates in the specimen total and by the three measures of influenza activity individually. For influenza intensity, the proportion of positive isolates of influenza virus in the specimen total, measured on the current day, was included in the model. For estimates by influenza epidemics, the dummy variables for influenza epidemics and for the epidemic-intermediate period were included in the model in order to adjust for the effect of influenza epidemics. For measures by influenza predominance, the dummy variables for influenza predominance and for the predominant-intermediate period were included in the model in order to adjust for the effect of influenza predominance compared with the predominance baseline period. The ERs of mortality and hospitalization associated with increases in air pollutants with adjustment for RSV and influenza were then calculated. Subsequently, the ERs calculated in Model 1 were compared with the ERs calculated in Model 3 in order to determine whether there were any confounding effects of influenza. We determined evidence for confounding by calculating if the absolute difference between the unadjusted and adjusted ER for influenza activity was > 0.1%. If that was the case, we regarded influenza activity as a confounder of the association between air pollution and health outcomes.

Modifying Effects of Influenza: Model 4

To study the modifying effect of influenza on the association between air pollution and health outcomes, each interaction term — defined as a product of the pollutant and the respective influenza measures — was added to Model 3. The corresponding interaction term for the pollutant and each of the influenza measures was examined. The ERs associated with the baseline effects and the interaction effects of air pollution were estimated.

ASSESSMENT OF AIR POLLUTION EFFECT BY LEVELS OF SOCIAL DEPRIVATION

For town planning purposes, the Hong Kong Special Administrative Region was divided in 2001 into 276 TPUs. The sizes of the TPUs vary, as well as the size of the population, which ranges from 0 to 203,616. Our analysis included all TPUs, except for suburban TPUs (n = 67) in the New Territories and outer islands of Hong Kong, which are remote and have population densities of less than the lowest quartile (533/km^2) of the population density of the whole territory of Hong Kong. Residents in these sparsely populated areas, accounting for about 1.5% of the total population, are usually exposed to sources and levels of air pollution different from those in urban areas.

The Census and Statistics Department of Hong Kong conducts a population census every five years. The TPU is the smallest unit of land area in the population census report. The 2001 census report contains 44 statistics for the Hong Kong population measured at the TPU level. We performed factor analyses on 18 socioeconomic and demographic variables related to social deprivation available from this population census database. Six factors, accounting for 69% of the variation, were extracted by principal component analysis. Based on the distribution of factor loadings, we chose six variables to describe the conditions of social deprivation for each TPU: the proportion of the population with unemployment, monthly household income < U.S. $250, no schooling at all, one-person household, never-married status, and subtenancy. Each of these six variables had significant factor loading for a specific principal factor, and all of them are deemed to be representative indicators of social disadvantage in the published literature and in the setting of the Hong Kong population. The first four of these conditions are more or less related to a lack of material resources. The next condition, being unmarried, may be regarded as undesirable in a social and family context in Chinese society. In Hong Kong, subtenancy specifically applies to people who cannot afford to rent a whole flat and who may rent a part (usually a small room) of a flat from another tenant.

The SDI for each TPU was calculated by taking the average of these six variables. A detailed description of the development of the SDI is given in a previous study (Wong CM et al. 1999a), which showed that each of these six measures was correlated with a standard mortality rate at the TPU level and that mortality was high in TPUs with a high SDI.

Each TPU was assigned to one of three groups based on what part of the index it fell into: low (less than the lowest tertile of SDI), middle (the lowest tertile to the middle tertile), and high (greater than the highest tertile). In these three SDI groups, respectively, the crude death rates per 100,000 population were 86.1, 126.2, and 162.7 for CVD, and 53.4, 82.9, and 114.3 for RD. The corresponding hospitalization rates were 527.1, 638.8, and 951.9 for CVD, and 652.6, 777.2, and 1066.5 for RD (Appendix G).

We performed Poisson regressions (using Model 1) for each SDI level for both mortality and hospitalization data, and also for each district where an air pollution monitoring station was available for hospitalization data. (There are a total of eight district boards, each with a monitoring station.) In stratified analyses by SDI levels, each of which may be spread over several districts, daily air pollutant concentrations were computed by taking the average of measurements from the eight monitoring stations, following the usual approach for measuring exposure in daily time-series studies. But in the analysis by district board, daily air pollutant concentrations were based on the individual monitoring station located in each district.

We used a case-only approach to assess the potential interaction between SDI level and ambient air pollution on mortality. The case-only approach has been commonly used to study environment–gene interaction. However, recently, this approach has been applied to determine the interaction between time-varying factors and other individual factors (Armstrong 2003; Schwartz 2005). The change in relative risk from air pollution given different SDI levels is calculated based on the relationship between social deprivation level and the levels of ambient air pollution on the date of death using multinomial logistic regression. Multinomial regression has recently been applied by us in another study comparing the effects of air pollution on subjects exercising at different levels (Wong CM et al. 2007). In that study, a case-only approach with a logit model was fitted to determine whether the health effects of air pollution increased with an increase in SDI level. All analyses were performed using the statistical software package R, version 2.5.1 (R Development Core Team 2007) and with mgcv, version 1.3-25.

A summary of the technical details pertaining to this study is presented in Appendix A, including information on the software package, explicit codes used in the main statistical model, degrees of freedom per year used for the smoothing of time in the main regression model, the value of the overdispersion parameter, and whether the deviance parameter was scaled or unscaled.

Table 3. Summary Statistics of Daily Mortality, 1996–2002

Mortality Outcome	Deaths per Day						
	Minimum	1st Quarter	Median	Mean	3rd Quarter	Maximum	SD
All natural causes							
All ages	48	75	83	84.2	92	135	12.8
65+	36	57	64	65.4	72	113	11.6
0–4	0	0	0	0.6	1	5	0.8
5–44	0	2	4	3.8	5	14	2.0
45–64	4	12	14	14.3	17	30	3.9
Cardiovascular	6	19	23	23.8	28	54	6.5
Stroke	0	7	9	8.9	11	22	3.3
Cardiac or heart disease	2	9	12	12.0	14	29	4.1
Respiratory	3	12	16	16.2	19	34	5.2
LRI	0	7	9	9.3	12	24	3.7
COPD	0	4	6	5.9	8	19	2.9
Accidental	0	3	4	4.2	6	14	2.2
Non-cardiopulmonary and nonaccidental	23	39	44	44.2	49	76	7.3

Table 4. Summary Statistics of Daily Hospitalizations, 1996–2002

Hospitalization Outcome	Admissions per Day						
	Minimum	1st Quarter	Median	Mean	3rd Quarter	Maximum	SD
Cardiovascular							
All ages	75	166	202	203.5	241	345	48.5
65+	47	108	128	130.8	152	222	30.1
Stroke							
All ages	13	40	46	47.1	54	88	10.0
IHD							
All ages	15	36	46	46.1	55	93	13.1
Respiratory							
All ages	143	230	266	270.3	303	586	56.3
65+	57	112	135	138.5	160	302	36.7
ARD							
All ages	48	84	99	104.9	122	275	29.8
0–14	22	46	56	60.1	72	149	19.5
ALRI							
All ages	15	35	44	46.4	56	124	15.4
65+	1	11	15	17.3	21	63	8.9
COPD							
All ages	41	77	89	91.5	104	176	20.0
65+	19	48	58	59.6	70	124	16.7
Asthma							
All ages	7	21	26	26.7	31	67	8.5
0–14	1	8	11	12.7	16	51	6.3

RESULTS

MORTALITY AND HOSPITALIZATION

Tables 3 and 4 show the distributions of daily mortality and hospitalization outcomes, including the 25th, 50th, and 75th percentiles. The mean daily count of cardiovascular-related mortality (23.8 deaths/day) was higher than that of respiratory-related mortality (16.2 deaths/day) (Table 3). Time-series plots of major mortality outcomes are shown in Figures 1A–C. Except for those due to the control causes, deaths peaked sharply during the first two months of the year. There was no clear pattern for respiratory mortality in 1997. On the other hand, the mean daily number of cardiovascular-related hospitalizations (203.5/day) was lower than that of respiratory-related hospitalizations (270.3/day) (Table 4). Time-series plots of cardiovascular-related hospitalizations showed a steadily increasing trend in males (M) and females (F) (Figure 2). As was the case with mortality, there was no clear pattern for hospitalizations for respiratory-related causes in 1997.

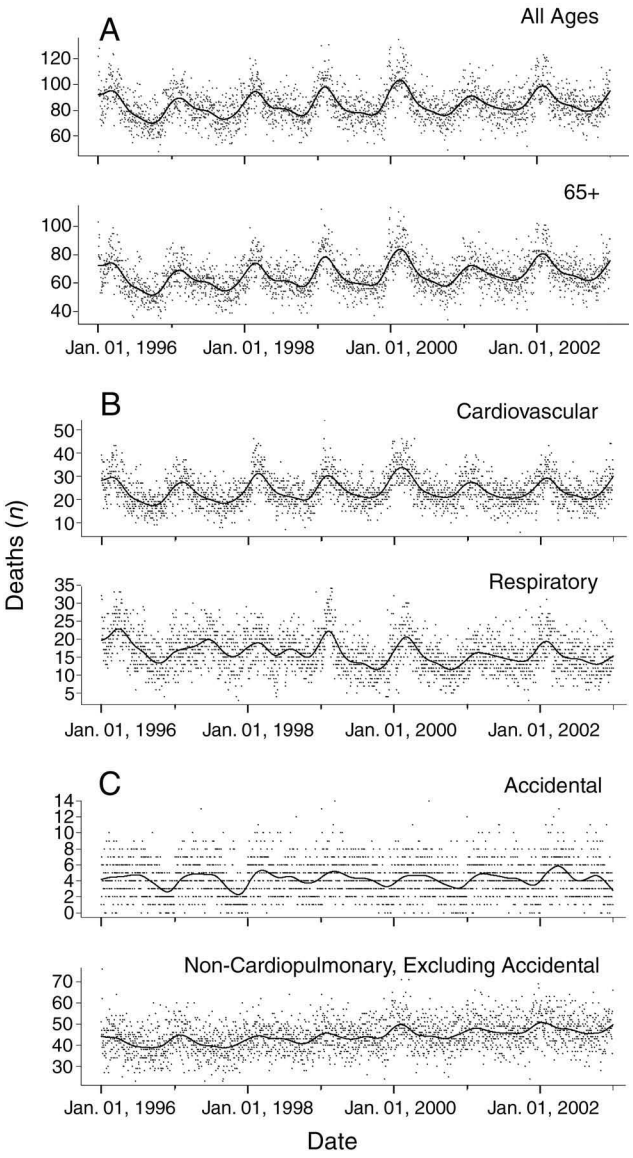

Figure 1. Time-series plots for daily mortality, using cubic smoothing splines with 35 df. (A) All natural causes; **(B)** cardiovascular- and respiratory-related causes; **(C)** control diseases.

AIR POLLUTANTS

The mean concentrations (and standard deviations) of NO_2, SO_2, PM_{10}, and O_3 in this study were 58.7 (20.0), 17.8 (12.1), 51.6 (25.3), and 36.9 (23.0) $\mu g/m^3$, respectively (Table 5). PM_{10} showed the highest variation among the four criteria pollutants. In terms of the standard deviation-to-mean ratio, SO_2 (0.68) showed the largest relative dispersion. Time-series plots of the concentration of each pollutant from the eight monitoring stations are shown in Figure 3. Data from each of the stations were included after applying the criterion of 75% measurement completion during the whole study period. For NO_2 and PM_{10}, peaks occurred during the winter season at most of the stations, with the exception of NO_2 at station 2. For SO_2 and O_3, there was no clear pattern for most of the stations.

The correlations between monitoring stations for the four pollutants ranged from 0.40 to 0.96 (Table 6). PM_{10} showed the highest correlation (range, 0.84 to 0.96), while SO_2 exhibited the lowest correlation between stations (range, 0.40 to 0.83). A sharp increase in SO_2 in two monitoring stations (stations 6 and 8) in 1999 was evident from the time-series plots. When these two stations were excluded from the calculation of daily concentration for the whole territory of Hong Kong, the resulting SO_2 concentration

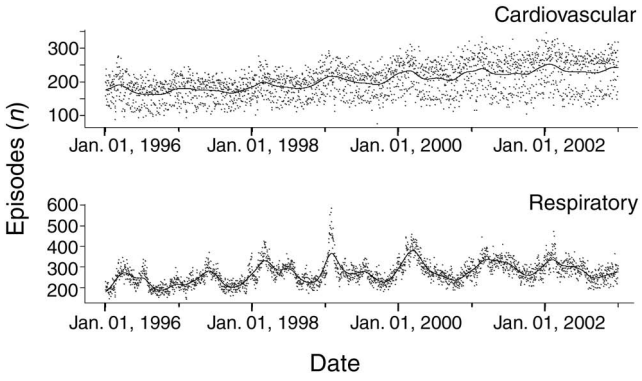

Figure 2. Time-series plots of cardiovascular-related (all ages, M + F) and respiratory-related (all ages, M + F) hospitalizations, using cubic smoothing splines with 42 df.

Table 5. Summary Statistics of Daily Pollutants (μg/m^3) and Meteorologic Data

	Minimum	1st Quarter	Median	Mean	3rd Quarter	Maximum	SD
NO_2	10.1	45.1	56.3	58.7	69.6	168.0	20.0
SO_2	1.8	9.6	14.7	17.8	22.1	109.4	12.1
PM_{10}	13.5	31.8	45.5	51.6	66.7	188.5	25.3
O_3	−8.2[a]	19.2	31.7	36.9	50.8	196.6	23.0
Temperature (^{0}C)	6.9	19.8	24.7	23.7	27.8	33.8	4.9
RH (%)	27.0	74.0	79.0	77.9	84.0	97.0	10.0

[a] Negative values occur in the centered data when the deviations of the original values from the individual station mean are greater than the overall mean of all stations.

was highly correlated with the concentration at the two stations (r = 0.98 for the whole period, with a range of 0.96 to 0.99 for year-by-year estimates; data not shown).

Table 7 shows the correlations of concentrations between pollutants by monitoring station, and the table in Appendix H lists the correlations of concentrations in all stations combined, with and without seasonal adjustments. For individual stations, the correlations between NO_2 and PM_{10} were the highest (range, 0.65 to 0.80), compared with those between other pairs of pollutants (all 0.63 or below). The correlations between NO_2 and SO_2 (range, 0.19 to 0.63) were slightly higher than those between PM_{10} and SO_2 (range, 0.18 to 0.55). The correlations of O_3 with NO_2 showed great variation (range, −0.07 to 0.41), those with SO_2 were mostly negative (range, −0.47 to 0.15), and those with PM_{10} were all positive and higher than those with the other pollutants (range, 0.35 to 0.55).

With seasonal adjustments, the correlations between pollutant concentrations estimated from all stations combined (Appendix H) showed patterns similar to those of concentrations for individual stations. With seasonal adjustments, the patterns of correlations between pollutants were also similar to those without seasonal adjustment, except they were higher between NO_2 and SO_2 and lower between NO_2 and PM_{10} and between SO_2 and PM_{10} (Appendix H).

SHORT-TERM EFFECTS OF AIR POLLUTION ON MORTALITY AND HOSPITAL ADMISSIONS

We assessed the main effects of the four criteria air pollutants on mortality and hospital admissions.

Mortality

Table 8 shows the ER (%) per 10-μg/m^3 increase in average concentration of lag 0–1 day for each pollutant individually (with 95% confidence intervals [CI]).

NO_2 The ERs (%) of mortality associated with NO_2 were 1.03 for all natural causes, 1.38 for CVD, and 1.41 for RD for all ages and were relatively higher, ranging from 1.16 to 1.54 for these three groups, for those 65 and older (65+) in age. These associations were all statistically significant. Mortality for the subcategories of CVD — cardiac (or heart) disease and stroke — and subcategories of RD — lower respiratory infections (LRI) and chronic obstructive pulmonary disease (COPD) — were also statistically significantly associated with NO_2 with ERs (%) ranging from 1.13 to 2.08, in all ages.

SO_2 The ERs (%) of mortality associated with SO_2 were 0.91 for all natural causes, 1.23 for CVD, and 1.31 for RD for all ages and were relatively higher for these three groups in the 65+ age group (except for RD), ranging from 1.05 to 1.44. The ER (%) for cardiac disease, a subcategory of CVD, was 2.72 and for LRI, a subcategory of RD, was 2.21, both for all ages. These associations were all statistically significant.

PM_{10} The ERs (%) of mortality associated with PM_{10} were 0.51 for all natural causes, 0.63 for CVD, and 0.69 for RD for all ages and were slightly higher for these three groups in the 65+ age group, ranging from 0.58 to 0.72. The ERs (%) for cardiac disease and stroke, subcategories of CVD, were 0.96 and 0.81, respectively, and for the RD subcategory of LRI, the ER (%) was 1.11, for all ages. These associations were all statistically significant.

O_3 The ERs (%) of mortality associated with O_3 were statistically significant only for all natural causes and for CVD for all ages, with estimates of 0.34 and 0.63, respectively. Statistically significant ERs were not found for all the other causes of death and age groups under study.

Table 6. Spearman Correlations Between Monitoring Stations by Pollutant

Pollutant / Monitoring Station	ST1	ST2	ST3	ST4	ST5	ST6	ST7	ST8
NO_2								
ST1	1.00	0.60	0.80	0.83	0.76	0.71	0.80	0.85
ST2	—	1.00	0.65	0.54	0.69	0.59	0.62	0.66
ST3	—	—	1.00	0.87	0.70	0.72	0.87	0.81
ST4	—	—	—	1.00	0.72	0.71	0.91	0.84
ST5	—	—	—	—	1.00	0.84	0.74	0.78
ST6	—	—	—	—	—	1.00	0.73	0.76
ST7	—	—	—	—	—	—	1.00	0.85
ST8	—	—	—	—	—	—	—	1.00
SO_2								
ST1	1.00	0.57	0.56	0.71	0.63	0.48	0.55	0.53
ST2	—	1.00	0.56	0.78	0.73	0.53	0.83	0.40
ST3	—	—	1.00	0.57	0.60	0.48	0.50	0.44
ST4	—	—	—	1.00	0.70	0.46	0.77	0.45
ST5	—	—	—	—	1.00	0.54	0.66	0.40
ST6	—	—	—	—	—	1.00	0.47	0.60
ST7	—	—	—	—	—	—	1.00	0.50
ST8	—	—	—	—	—	—	—	1.00
PM_{10}								
ST1	1.00	0.89	0.95	0.96	0.95	0.91	0.94	0.91
ST2	—	1.00	0.89	0.93	0.91	0.89	0.91	0.84
ST3	—	—	1.00	0.96	0.94	0.91	0.93	0.87
ST4	—	—	—	1.00	0.95	0.92	0.95	0.90
ST5	—	—	—	—	1.00	0.94	0.95	0.92
ST6	—	—	—	—	—	1.00	0.91	0.92
ST7	—	—	—	—	—	—	1.00	0.92
ST8	—	—	—	—	—	—	—	1.00
O_3								
ST1	1.00	0.80	NA	0.88	0.86	0.79	0.84	0.79
ST2	—	1.00	NA	0.81	0.83	0.71	0.83	0.69
ST3	—	—	NA	NA	NA	NA	NA	NA
ST4	—	—	—	1.00	0.86	0.80	0.90	0.81
ST5	—	—	—	—	1.00	0.87	0.85	0.77
ST6	—	—	—	—	—	1.00	0.77	0.85
ST7	—	—	—	—	—	—	1.00	0.78
ST8	—	—	—	—	—	—	—	1.00

NA indicates not applicable (data on O_3 from station 3 was excluded from the analysis because the hourly data were less than 75% complete during the study period); ST indicates station.

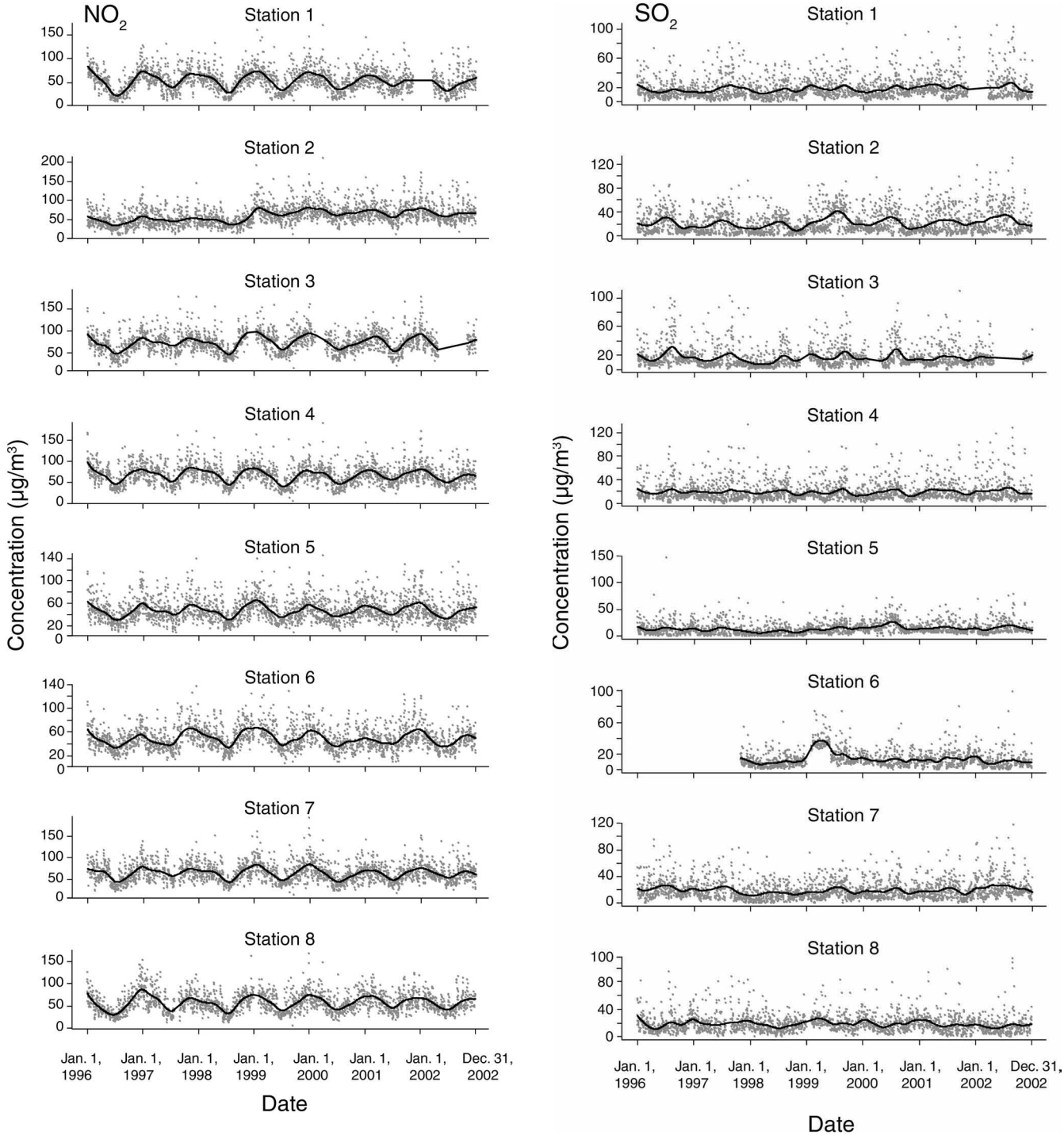

Figure 3. Time-series plots for daily pollutants NO_2, SO_2, PM_{10}, and O_3 for each of the eight monitoring stations, using cubic smoothing splines with 35 df. Data on O_3 from station 3 was excluded from the analysis because the hourly data was less than 75% complete during the study period.

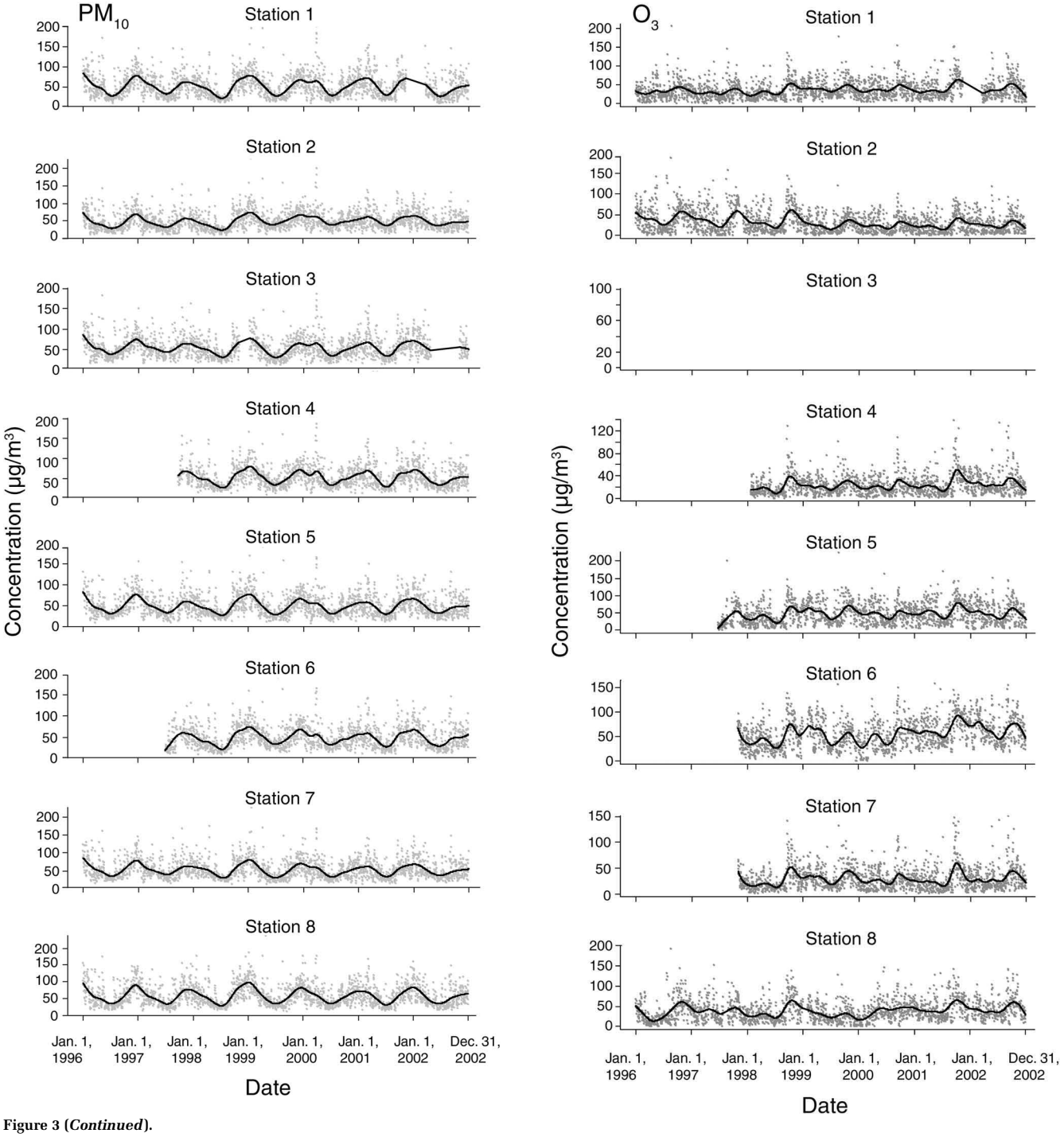

Figure 3 (*Continued*).

Table 7. Spearman Correlations Between Pollutants by Monitoring Stations

Monitoring Station / Pollutant	NO_2	SO_2	PM_{10}	O_3
ST1				
NO_2	1.00	0.39	0.78	0.18
SO_2	—	1.00	0.31	−0.04
PM_{10}	—	—	1.00	0.44
O_3	—	—	—	1.00
ST2				
NO_2	1.00	0.51	0.65	−0.07
SO_2	—	1.00	0.26	−0.47
PM_{10}	—	—	1.00	0.35
O_3	—	—	—	1.00
ST3				
NO_2	1.00	0.27	0.80	NA
SO_2	—	1.00	0.26	NA
PM_{10}	—	—	1.00	NA
O_3	—	—	—	NA
ST4				
NO_2	1.00	0.19	0.77	0.41
SO_2	—	1.00	0.18	−0.13
PM_{10}	—	—	1.00	0.52
O_3	—	—	—	1.00
ST5				
NO_2	1.00	0.42	0.65	0.15
SO_2	—	1.00	0.21	−0.10
PM_{10}	—	—	1.00	0.55
O_3	—	—	—	1.00
ST6				
NO_2	1.00	0.57	0.67	0.28
SO_2	—	1.00	0.45	0.12
PM_{10}	—	—	1.00	0.54
O_3	—	—	—	1.00
ST7				
NO_2	1.00	0.28	0.78	0.35
SO_2	—	1.00	0.18	−0.25
PM_{10}	—	—	1.00	0.45
O_3	—	—	—	1.00
ST8				
NO_2	1.00	0.63	0.79	0.41
SO_2	—	1.00	0.55	0.15
PM_{10}	—	—	1.00	0.48
O_3	—	—	—	1.00

NA indicates not applicable (data on O_3 from station 3 was excluded from the analysis because the hourly data was less than 75% complete during the study period); ST indicates station.

Hospitalization

Table 9 shows the ER (%) of hospitalization per 10-μg/m^3 increase in concentration at lag 0–1 day for each of the following single pollutants (including 95% CI).

NO_2 The ERs (%) of hospitalization associated with NO_2 for CVD and RD were 1.00 and 0.75 in the all-ages group and were relatively higher in the 65+ age group (1.19 and 0.90, respectively). For the RD subcategories of acute respiratory diseases (ARD), acute lower respiratory infections (ALRI), COPD, and asthma, the ERs (%) ranged from 0.76 to 1.94 for all ages. For COPD in the 65+ age group and asthma in the 0–14 age group, the ERs (%) were 1.52 and 1.22, respectively. These associations were all statistically significant.

SO_2 The ER (%) of hospitalization associated with SO_2, for CVD was 0.98 for all ages and 1.25 for the 65+ age group, both statistically significant. The ERs for hospitalization due to stroke and due to all subcategories of RD, except COPD in the all-ages group, were not statistically significant.

PM_{10} The ERs (%) of hospitalization associated with PM_{10} for CVD and RD were 0.58 and 0.60, respectively, in the all-ages group and were relatively higher at 0.68 and 0.70 in the 65+ age group. For the CVD subcategory of ischemic heart disease (IHD), the ER (%) was 0.72 for all ages. For RD subcategories of ARD, ALRI, COPD, and asthma, the ER (%) ranged from 0.66 to 1.32 for all ages. The ER (%) for ALRI in the 0–14 age group was 0.73; for COPD in the 65+ age group, it was 1.03; and for asthma in the 0–14 age group, it was 1.09. These associations were all statistically significant.

O_3 The ERs (%) of hospitalization associated with O_3 for CVD, including all subcategories, were not statistically significant. However, for RD, including all subcategories, the ER (%) ranged from 0.70 to 1.55 in all the age groups under study, and the associations were statistically significant.

SENSITIVITY ANALYSES

Variations in Degrees of Freedom in Smoothing Function for Seasonality and Time Trend

For most mortality outcomes, the ERs associated with NO_2 and SO_2 were stable using 5 to 12 df. However, using 4 df, the ERs (%) associated with NO_2 were slightly higher (by 0.05 on average; range, 0.01 to 0.1) and those associated with SO_2 were substantially higher (by 0.19 on average; range, 0.1 to 0.31) (Figures I.1–I.4 in Appendix I). ERs associated with PM_{10} and O_3 were stable throughout, using

Table 8. Air Pollution Effects on Mortality: ER (%) per 10-μg/m^3 Increase in Average Concentration of Pollutants at Lag 0–1 Day

Cause of Death / Age Group	NO_2		SO_2		PM_{10}		O_3	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
All Natural Causes								
All ages	1.03	(0.69 to 1.37)	0.91	(0.40 to 1.42)	0.51	(0.23 to 0.80)	0.34	(0.02 to 0.66)
65+	1.16	(0.77 to 1.54)	1.05	(0.47 to 1.63)	0.58	(0.26 to 0.91)	0.35	(−0.02 to 0.71)
Cardiovascular								
All ages	1.38	(0.75 to 2.01)	1.23	(0.27 to 2.21)	0.63	(0.11 to 1.16)	0.63	(0.04 to 1.23)
65+	1.54	(0.82 to 2.26)	1.44	(0.33 to 2.55)	0.66	(0.06 to 1.26)	0.64	(−0.05 to 1.32)
Cardiac or heart, all ages	2.08	(1.10 to 3.07)	2.72	(1.22 to 4.23)	0.96	(0.15 to 1.78)	0.61	(−0.32 to 1.54)
Stroke, all ages	1.13	(0.19 to 2.08)	1.08	(−0.36 to 2.53)	0.81	(0.03 to 1.60)	0.54	(−0.35 to 1.43)
Respiratory								
All ages	1.41	(0.67 to 2.15)	1.31	(0.21 to 2.43)	0.69	(0.08 to 1.31)	0.36	(−0.33 to 1.05)
65+	1.44	(0.66 to 2.21)	1.25	(0.09 to 2.42)	0.72	(0.08 to 1.36)	0.49	(−0.23 to 1.21)
LRI, all ages	1.75	(0.74 to 2.77)	2.21	(0.71 to 3.73)	1.11	(0.27 to 1.95)	0.41	(−0.52 to 1.35)
COPD, all ages	1.39	(0.18 to 2.61)	0.54	(−1.29 to 2.41)	0.40	(−0.59 to 1.41)	0.94	(−0.20 to 2.09)

Table 9. Air Pollution Effects on Hospitalization: ER (%) per 10-μg/m^3 Increase in Average Concentration of Pollutants at Lag 0–1 Day

Outcome Group / Age Group	NO_2		SO_2		PM_{10}		O_3	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Cardiovascular								
Heart disease								
All ages	1.00	(0.73 to 1.26)	0.98	(0.57 to 1.39)	0.58	(0.36 to 0.80)	0.12	(−0.12 to 0.37)
65+	1.19	(0.89 to 1.50)	1.25	(0.78 to 1.72)	0.68	(0.43 to 0.94)	0.09	(−0.20 to 0.37)
Stroke, all ages	0.33	(−0.09 to 0.76)	−0.17	(−0.80 to 0.47)	0.12	(−0.23 to 0.48)	−0.05	(−0.43 to 0.33)
IHD, all ages	0.94	(0.46 to 1.42)	0.93	(0.21 to 1.66)	0.72	(0.32 to 1.13)	0.26	(−0.17 to 0.69)
Respiratory								
All ages	0.75	(0.50 to 1.00)	0.13	(−0.24 to 0.50)	0.60	(0.40 to 0.80)	0.81	(0.58 to 1.04)
65+	0.90	(0.58 to 1.21)	0.08	(−0.38 to 0.54)	0.70	(0.44 to 0.96)	0.81	(0.52 to 1.11)
ARD								
All ages	1.22	(0.74 to 1.71)	0.55	(−0.18 to 1.29)	0.88	(0.49 to 1.28)	1.55	(1.11 to 1.99)
0–14	0.22	(−0.23 to 0.67)	0.00	(−0.67 to 0.67)	0.33	(−0.04 to 0.69)	0.70	(0.29 to 1.11)
ALRI								
All ages	0.76	(0.27 to 1.24)	0.09	(−0.64 to 0.83)	0.66	(0.26 to 1.05)	1.09	(0.64 to 1.54)
0–14	0.73	(−0.04 to 1.51)	0.34	(−0.82 to 1.52)	0.73	(0.11 to 1.35)	1.10	(0.39 to 1.81)
COPD								
All ages	1.94	(1.55 to 2.33)	0.70	(0.10 to 1.31)	1.32	(0.99 to 1.65)	1.54	(1.17 to 1.92)
65+	1.52	(1.09 to 1.96)	0.61	(−0.05 to 1.27)	1.03	(0.67 to 1.39)	0.99	(0.57 to 1.40)
Asthma								
All ages	0.96	(0.31 to 1.62)	−0.28	(−1.28 to 0.74)	0.81	(0.27 to 1.36)	1.53	(0.91 to 2.16)
0–14	1.22	(0.31 to 2.12)	0.15	(−1.25 to 1.57)	1.09	(0.35 to 1.84)	1.10	(0.25 to 1.96)

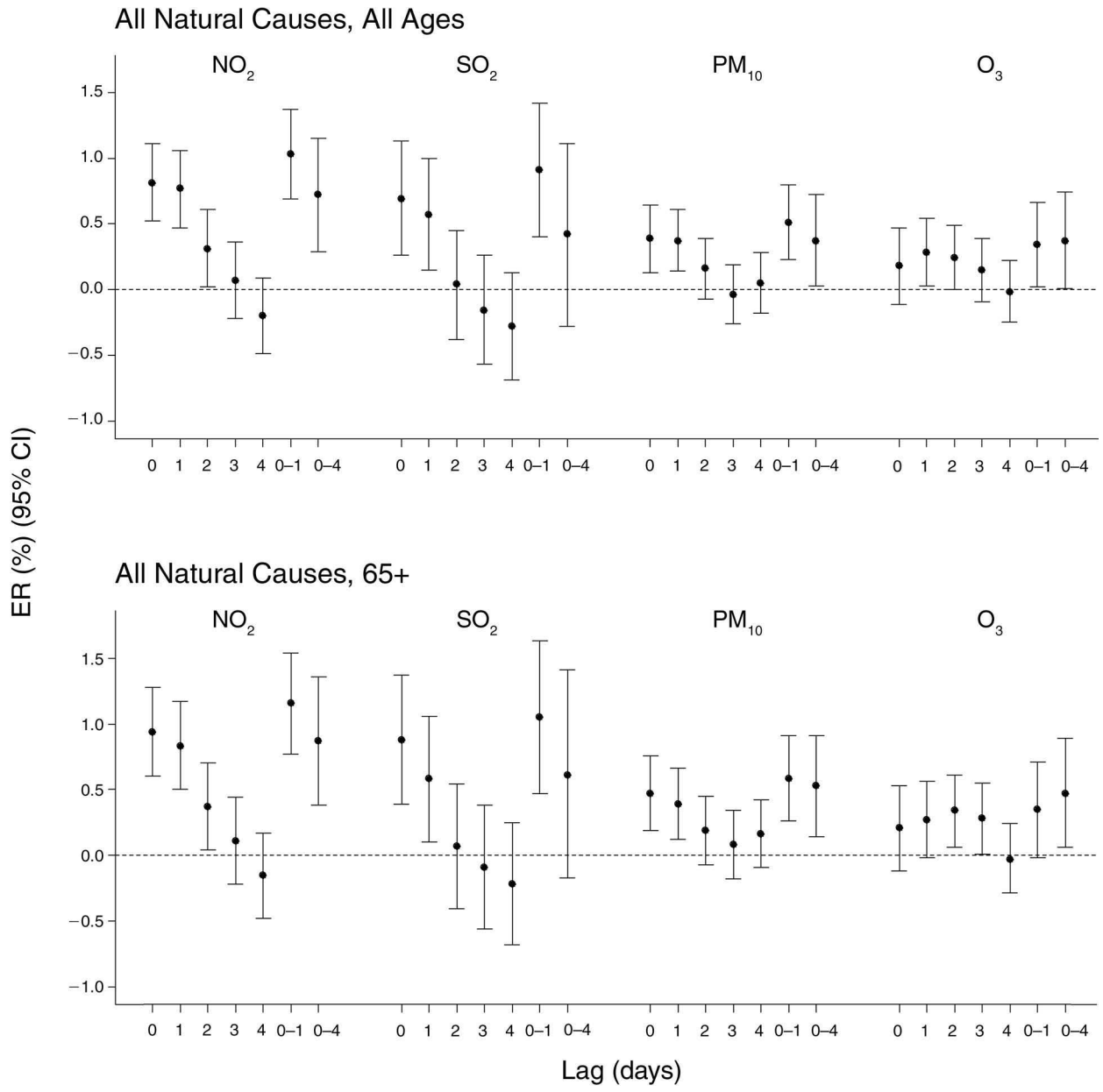

Figure 4. Lag patterns of major mortality outcomes (M + F) showing air pollution effects at single-lag days, lag 0–1 day, and lag 0–4 days for all natural mortality, all ages; for all natural mortality, 65+ years of age; for cardiovascular-related mortality, all ages; and for respiratory-related mortality, all ages.

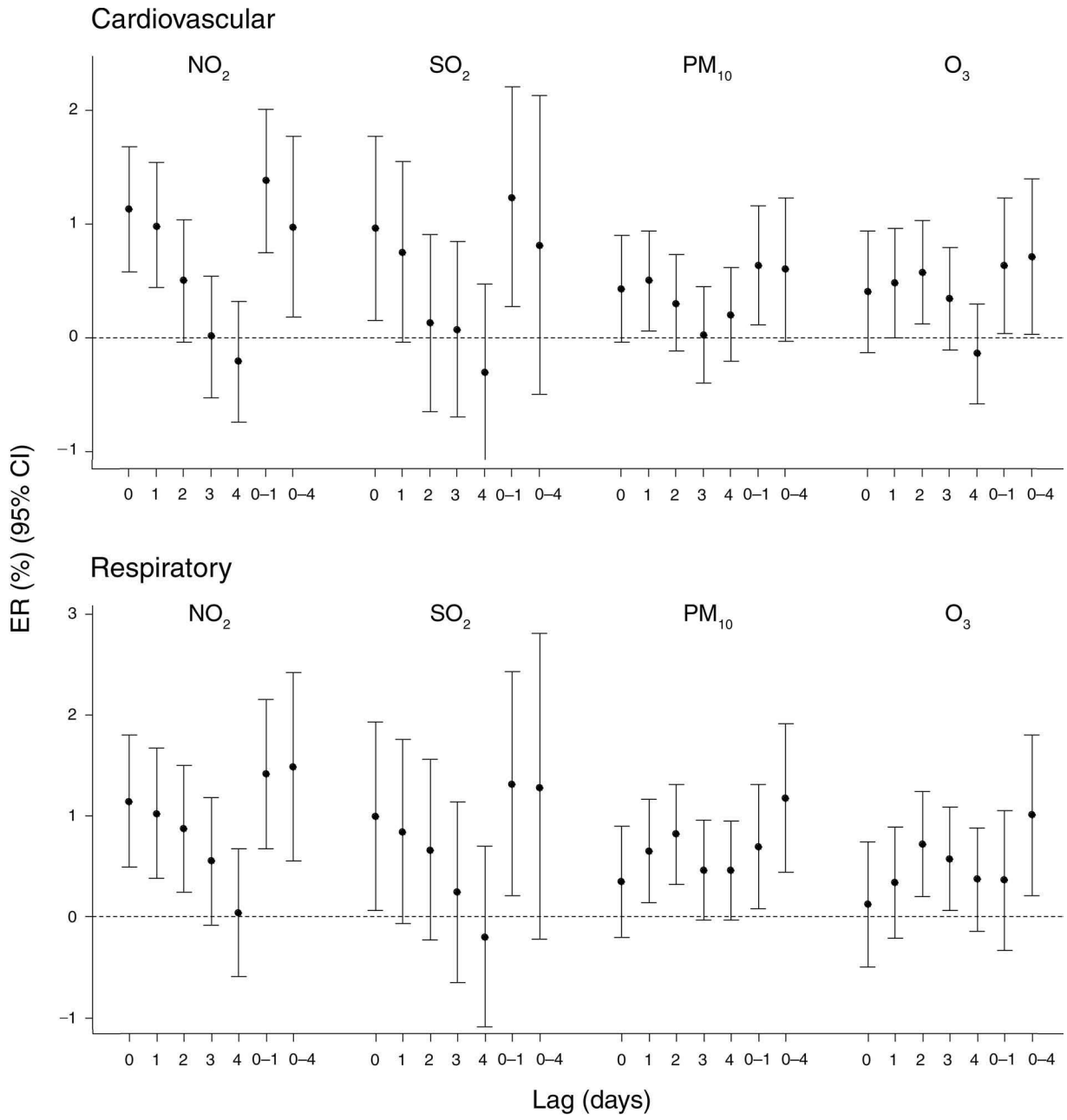

Figure 4 (*Continued*).

4 to 12 df. For cardiovascular- and respiratory-related hospitalization, the ERs associated with each pollutant using different degrees of freedom varied in a way similar to those for mortality (Figures J.1 and J.2 in Appendix J).

Lag Patterns of Single-Day Effects

Figure 4 shows the lag patterns of major mortality outcomes from the current day (lag 0) to lag 4 day (as well as the averages 0–1 and 0–4). For NO_2, the highest ER of mortality for all natural causes, including the subcategories of CVD and RD, occurred at the current day, and ER decreased to the lowest point at lag 4 day. For SO_2, the lag patterns of ER of mortality were similar to those for NO_2; they also showed the highest ER occurring at the current day. For PM_{10}, there were no trends in the ER of mortality for all categories of cause of death; the highest ER of mortality for different categories of cause of death occurred at different lag days. For O_3, the lag patterns of ERs showed a trend, with the highest effect occurring at either lag 1 or 2 days and then decreasing to an insignificant level at lag 4 days. The ER estimates for all the major mortality outcomes are shown in Tables K.1 and K.2 in Appendix K.

Figure 5 shows the lag patterns of major hospitalization outcomes from the current day (lag 0) to lag 4 day. For NO_2, ERs of hospitalization for CVD and RD also showed the highest estimates occurring at the current day, but they became stable after lag 1 day. For SO_2, the ERs of hospitalization for CVD and RD were not significant after lag 1 day. For PM_{10}, the lag patterns of ER of hospitalization for CVD and RD were similar to those for NO_2, showing the highest ER occurring at the current day. For O_3, the lag patterns for ERs of hospitalization for CVD and RD showed that the ER reached the highest value at lag 1 day, then dropped to a lower and statistically insignificant value at lag 4 day. The ER estimates for all the major hospitalization outcomes are shown in Tables L.1 and L.2 in Appendix L.

Temperature Effect

For most mortality outcomes, we adjusted for temperature at lag 1–2 days or 3–7 days, in addition to lag 0 day. We found that reductions in ER (%) were greater for NO_2 (0.5 on average; range, 0.4–0.7) than for SO_2 (0.2; range, 0.1–0.5), PM_{10} (0.1; range, 0.0–0.2), or O_3 (0.1; range, 0.1–0.2) (Appendix M).

Control Causes of Death

No statistically significant associations for any pollutants were found with accidental mortality; but some positive and statistically significant associations were found with mortality due to non-cardiopulmonary (nonaccidental) causes (see Table K.3 in Appendix K).

Concentration–Response Curves

For most mortality outcomes, NO_2 showed a concave shape, with the trough at about 50 $\mu g/m^3$, but SO_2 showed a convex shape, with a wider confidence interval (95% CI) for concentrations greater than 60 $\mu g/m^3$. PM_{10} showed a roughly linear relationship. O_3 showed an irregular but concave shape (Figure 6). For hospitalization outcomes, all pollutants showed some degree of linear relationship, except O_3 for CVD (Figure 7). The results of the concentration–response analysis agreed with the nonlinearity test results. Tests for nonlinearity were statistically significant only for NO_2 associated with all mortality and hospitalization outcomes, except for hospitalization due to CVD, and for SO_2 associated with mortality due to all natural causes (Table 10).

Table 10. Test for Nonlinearity for the Concentration–Response Curve[a]

	NO_2		SO_2		PM_{10}		O_3	
	χ^2	P	χ^2	P	χ^2	P	χ^2	P
Mortality								
All natural causes, all ages	17.73	***	6.51	*	1.56	NS	0.69	NS
All natural causes, 65+	20.62	***	6.62	*	0.73	NS	1.16	NS
Cardiovascular	16.37	***	3.91	NS	1.14	NS	1.51	NS
Respiratory	17.07	***	3.19	NS	0.36	NS	3.25	NS
Morbidity								
Cardiovascular	3.99	NS	12.50	NS	3.29	NS	6.84	NS
Respiratory	12.85	**	4.36	NS	8.76	NS	5.02	NS

[a] P values are for the deviance between a nonlinear model (with 3 df) and a linear model (with 1 df), following a χ^2 distribution (with 2 df). NS indicates not significant ($P > 0.05$); * $0.01 < P \leq 0.05$; ** $0.001 < P \leq 0.01$; *** $P \leq 0.001$.

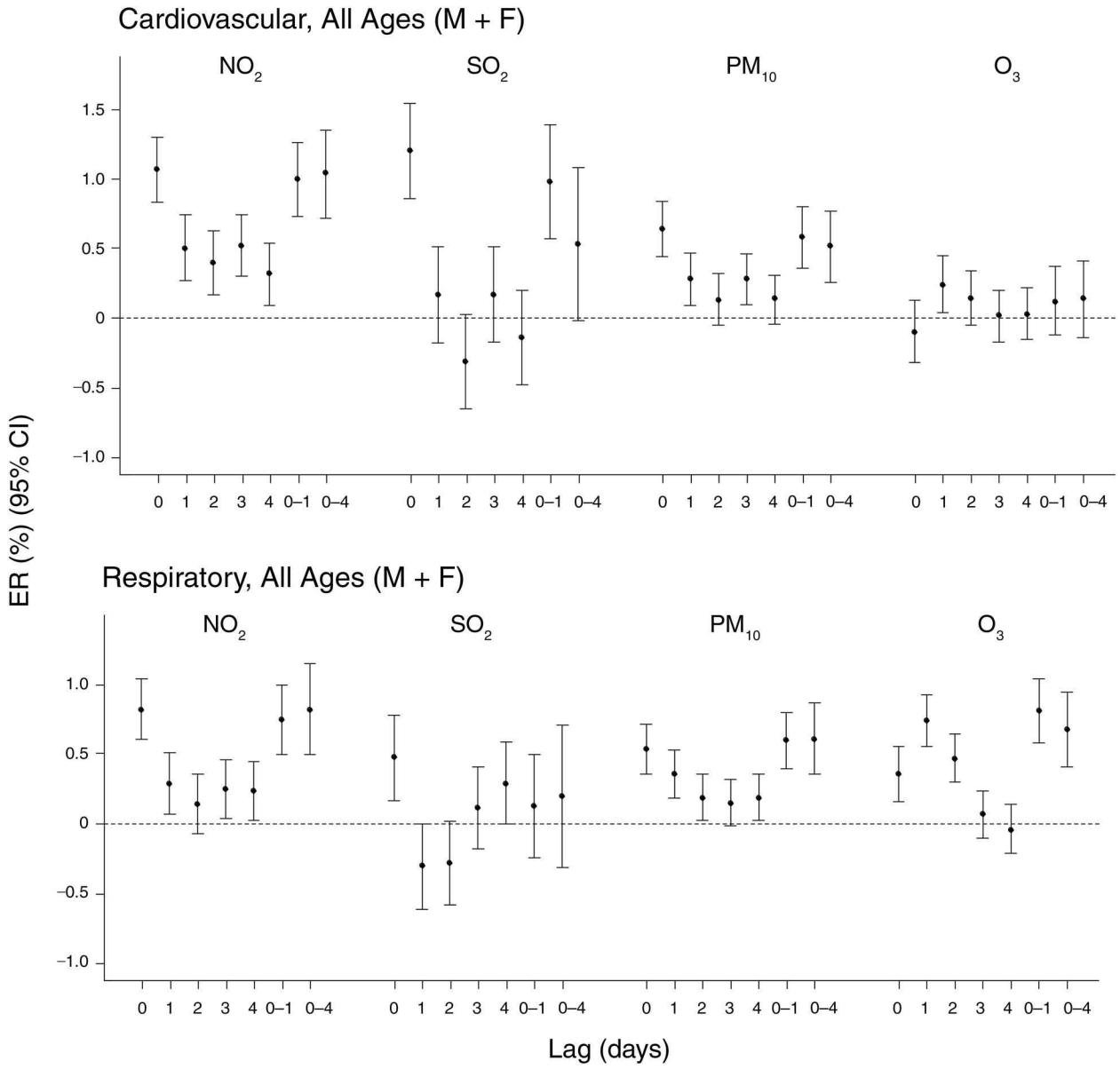

Figure 5. Lag patterns of major hospitalization outcomes showing air pollution effects at single-lag days, lag 0–1 day, and lag 0–4 days for cardiovascular-related hospitalization, all ages, M + F; and respiratory-related hospitalization, all ages, M + F.

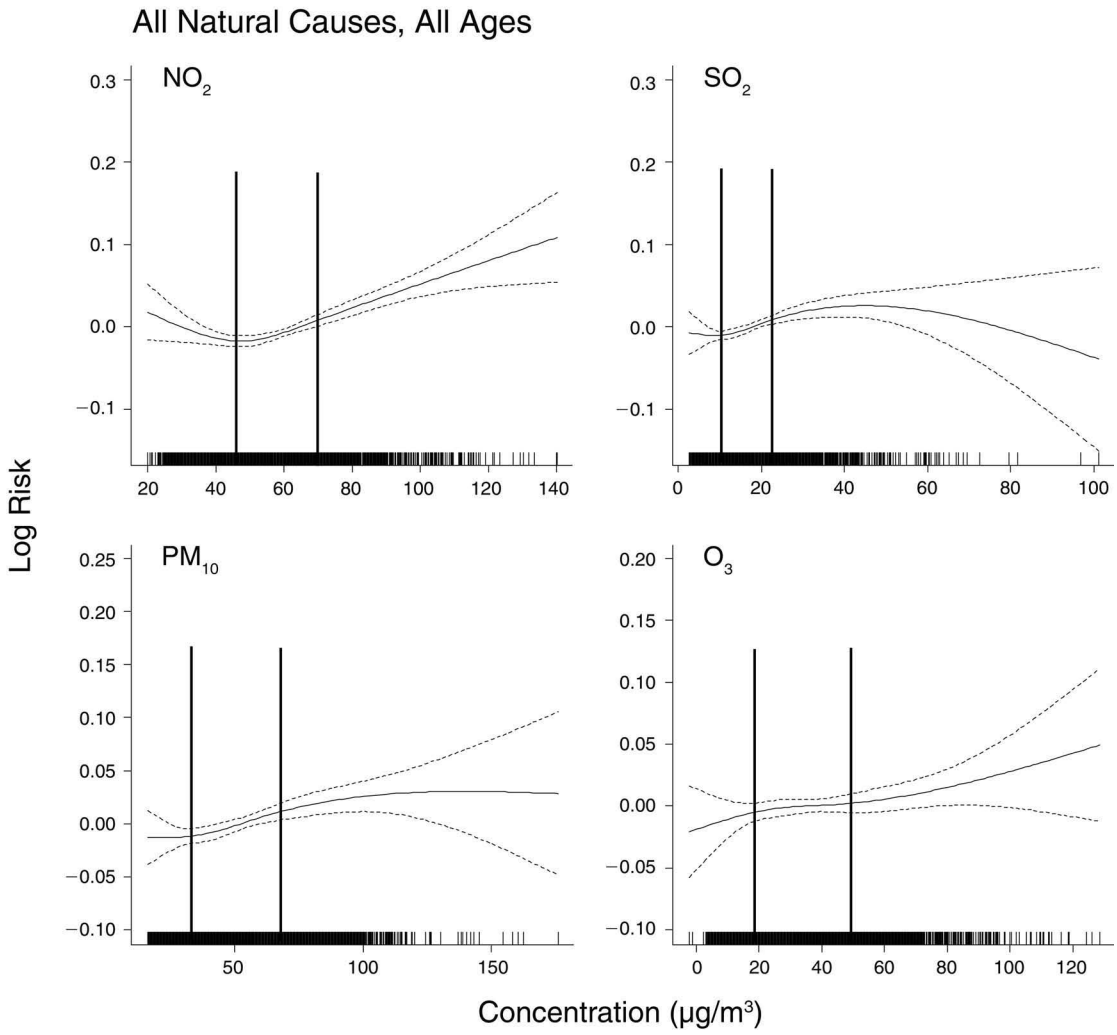

Figure 6. The concentration–response curves for mortality outcomes associated with NO_2, SO_2, PM_{10}, and O_3 for all natural causes, all ages; all natural causes, age 65+; cardiovascular-related causes, all ages; and respiratory-related causes, all ages. The two vertical lines represent the interquartile range of pollutant concentrations.

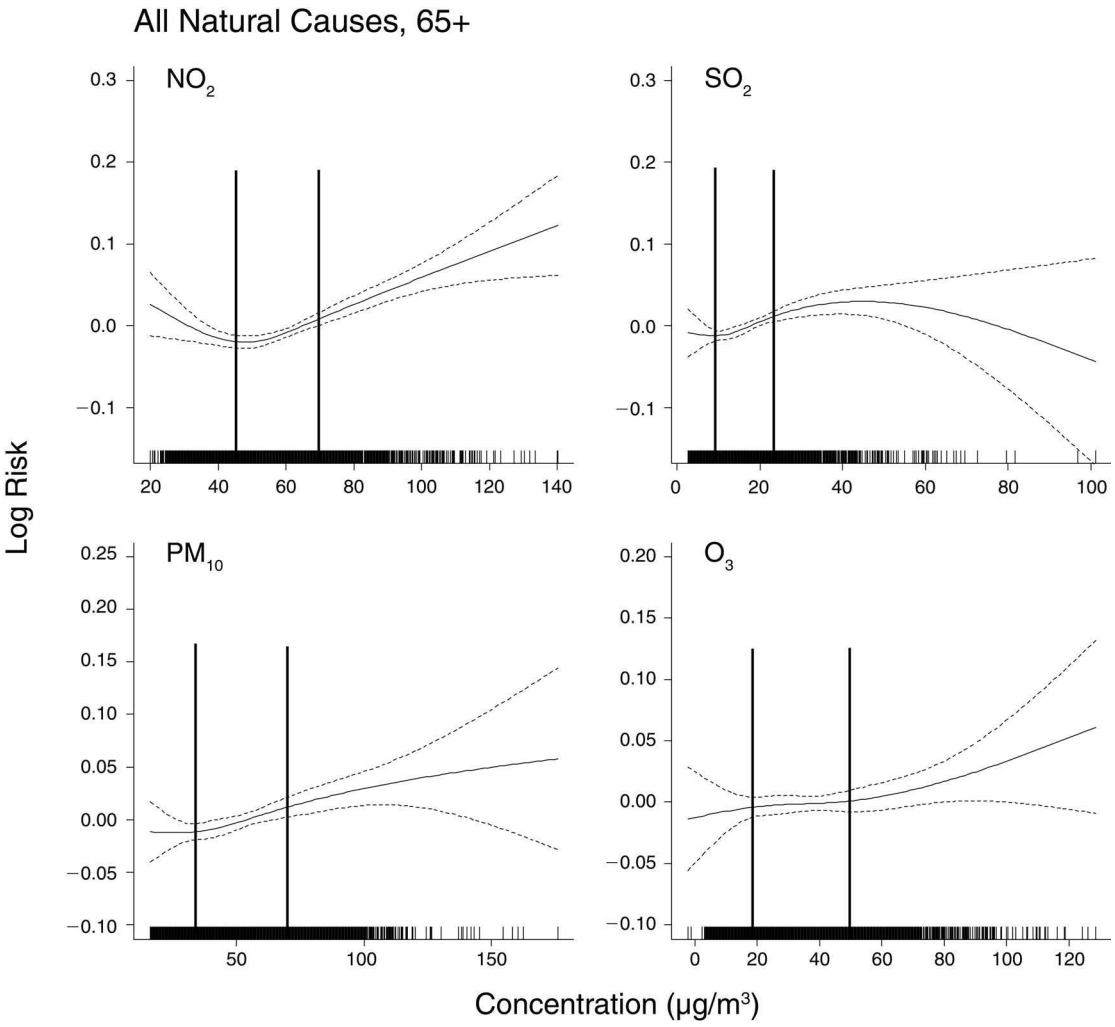

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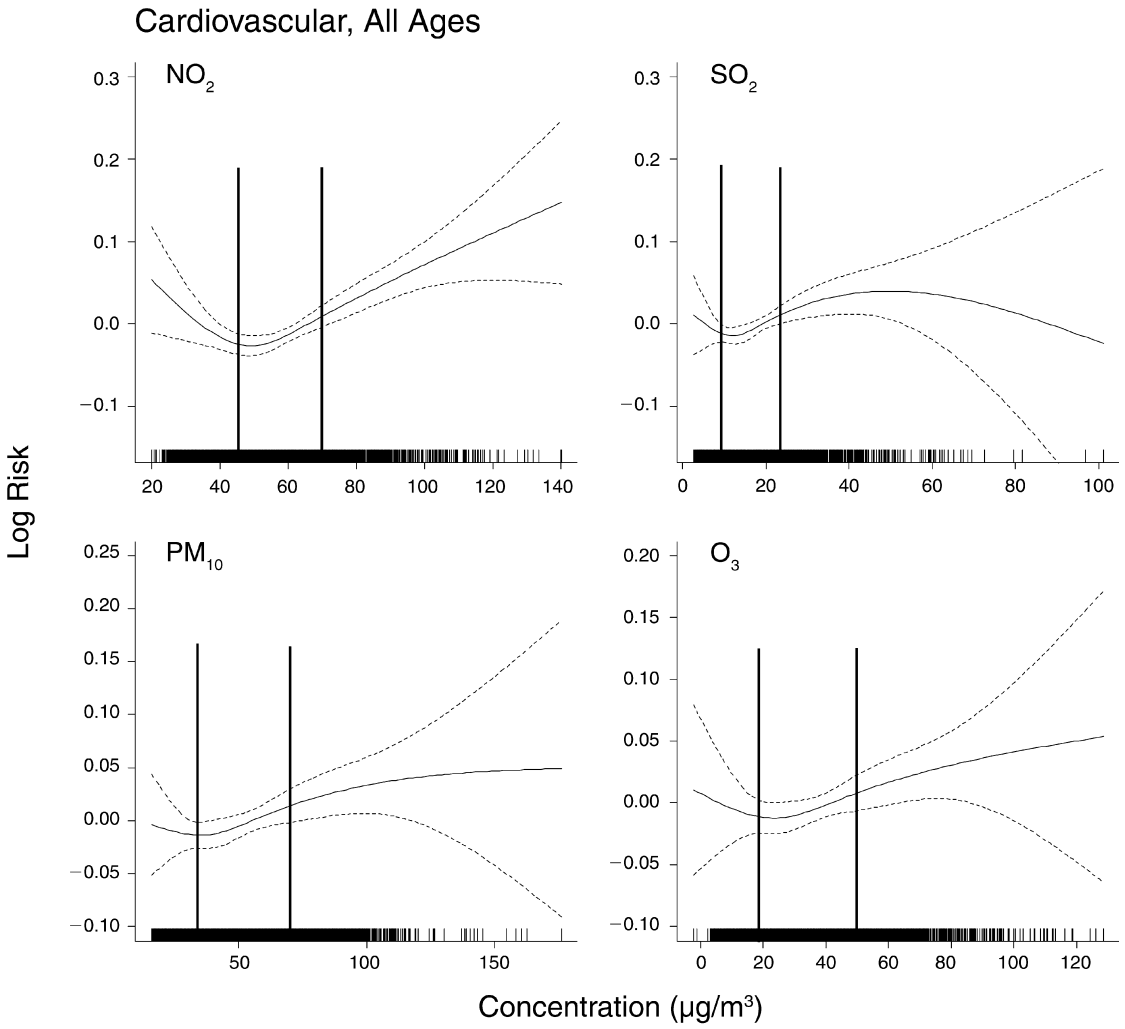
Figure 6 (*Continued*).



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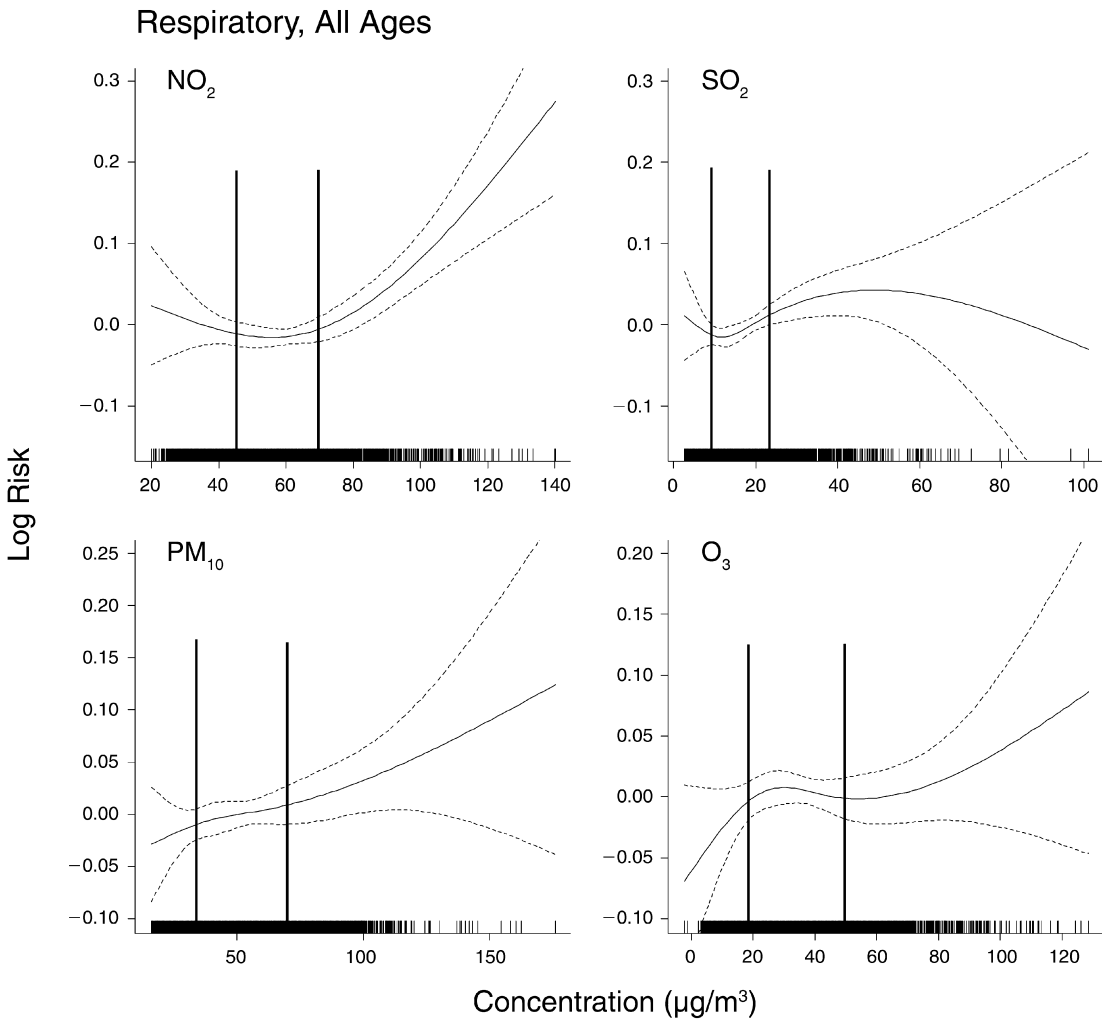

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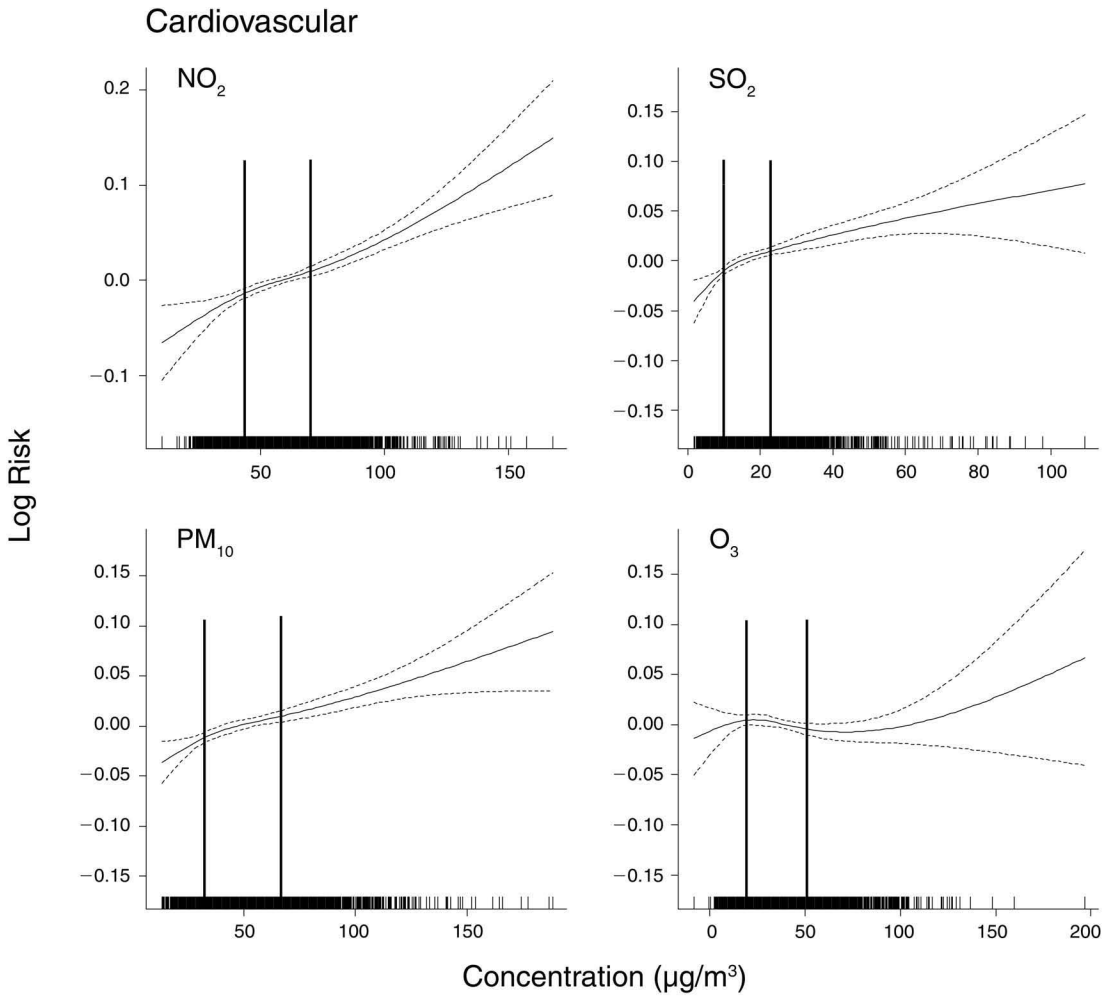

Figure 7. The concentration–response curves for hospitalization outcomes associated with NO_2, SO_2, PM_{10}, and O_3 for cardiovascular-related causes; and respiratory-related causes. The two vertical lines represent the interquartile range of pollutant concentrations.

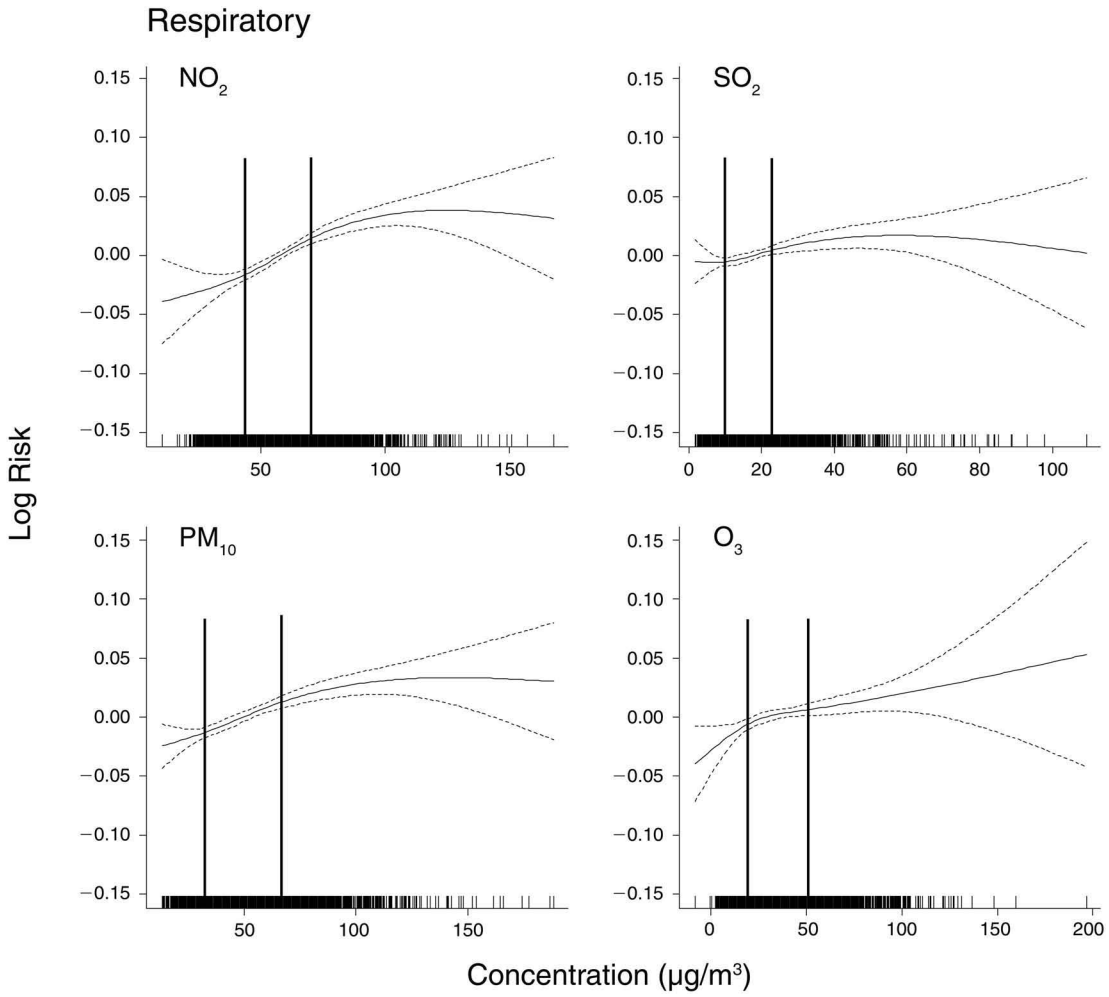

Figure 7 (*Continued*).

INFLUENZA-ASSOCIATED MORTALITY AND HOSPITAL ADMISSIONS

The weekly mean proportion of positive isolates was 10.1% for influenza A+B and 8.8% for RSV (data not shown). The circulation of influenza was apparently higher than that of RSV. The pattern of the weekly proportion (%) of positive isolates of influenza A+B in 1996–2002 showed that, except for 1997 and 2001, the seasonal pattern of influenza intensity comprised two peaks each year: one in the winter (January to March) and one in the summer (July to August) (Figure 8).

The ER of mortality and hospitalization for the three measures of influenza, relative to the corresponding reference levels, showed consistently statistically significant results for both CVD and RD with very few exceptions (see Tables 11 and 12).

All three measures of influenza activity showed consistently statistically significant ER of mortality for both CVD and RD (see Table 11 for CIs). For influenza intensity, a 10% change in the proportion of influenza-positive isolates was associated with an increase in ER (%) of 3.6 to 7.8 in CVD and its subcategories, and an increase of 4.1 to 9.5 in RD and its subcategories. For influenza epidemics, the ER (%) increased 9.4 to 19.3 in CVD and its subcategories, and 12.3 to 23.6 in RD and its subcategories relative to the epidemic baseline. For influenza predominance, the ER (%) increase ranged from 8.6 to 21.8 for CVD and its subcategories and from 14.1 to 23.4 for RD and its subcategories, relative to the predominance baseline.

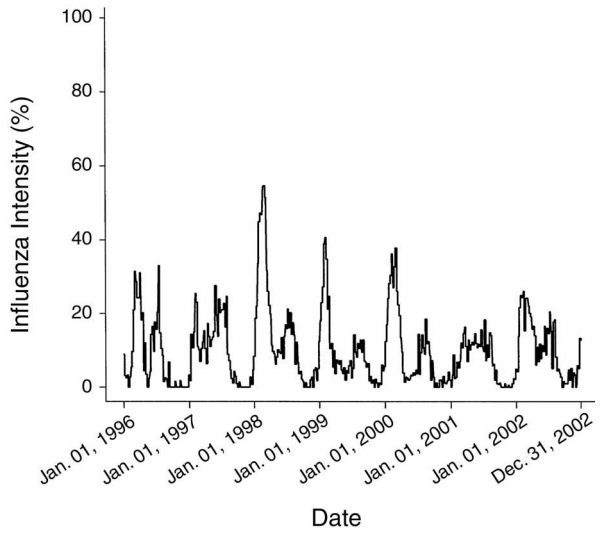

Figure 8. Weekly proportion of positive isolates of influenza A+B viruses from 1996–2002.

All three measures of influenza activity showed a statistically significant ER of hospitalization for both CVD and RD, except for stroke and asthma in the all-ages group (see Table 12 for CIs). The magnitude of the ER for asthma associated with the three measures of influenza was in the same negative direction, except that some estimates were not significant. For influenza intensity, the ER (%) associated with a 10% change in the proportion of positive influenza isolates ranged from 0.8 to 2.1 for CVD and its subcategories, and from 2.6 to 12.2 for RD and its subcategories except asthma. For influenza epidemics, the ER (%) increase ranged from 2.5 to 5.6 for CVD and its subcategories and from 6.6 to 39.4 for RD and its subcategories except asthma, relative to the epidemic baseline. For influenza predominance, the ER (%) increase ranged from 1.9 to 6.3 for CVD and its subcategories and from 6.2 to 35.8 for RD and its subcategories except asthma, relative to the predominance baseline.

CONFOUNDING EFFECTS OF INFLUENZA IN ESTIMATION OF HEALTH EFFECTS FROM AIR POLLUTION

Influenza intensity had a low correlation not only with meteorologic conditions (influenza intensity and temperature: $r = -0.15$; influenza intensity and RH: $r = 0.05$) but also with the four pollutants (influenza intensity and NO_2: $r = -0.22$; influenza intensity and O_3: $r = 0.2$; influenza intensity and PM_{10}: $r = -0.07$; influenza intensity and SO_2: $r = -0.31$) (data not shown). Mean influenza intensity was 10.05%, with a standard deviation of 1.01% (data not shown).

Mortality

Influenza epidemic compared with baseline There was no difference between the influenza epidemic and baseline periods in mean concentrations for all four pollutants (Table 13). Temperature was lower during the influenza epidemics than during baseline periods, but RH was higher. The daily mean mortality counts were higher during the influenza epidemics for each of the cause-specific groups compared with the baseline periods (Table 14).

Influence predominance compared with baseline There was no difference between the influenza predominance and baseline periods in mean concentrations for all four pollutants (Table 13). Temperature was lower during the influenza epidemic and predominance periods than during baseline periods, but RH was higher. The daily mean mortality counts were higher during the influenza predominance period for each of the cause-specific groups compared with the baseline periods (Table 14).

Table 11. Influenza Effects on Mortality: ER (%) in Three Measures of Influenza Activity Relative to the Corresponding Reference Levels[a] in the Current Week

Mortality Outcome	Influenza Intensity		Influenza Epidemic		Influenza Predominance	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Cardiovascular	5.13	(3.74 to 6.55)	13.32	(9.04 to 17.76)	12.64	(8.03 to 17.44)
Cardiac or heart disease	7.75	(5.60 to 9.93)	19.29	(12.49 to 26.49)	21.80	(14.27 to 29.84)
Stroke	3.59	(1.60 to 5.61)	9.44	(3.43 to 15.79)	8.55	(2.01 to 15.50)
Respiratory	4.83	(3.23 to 6.45)	12.34	(7.50 to 17.39)	14.07	(8.62 to 19.80)
LRI	4.11	(1.97 to 6.29)	12.83	(6.32 to 19.73)	15.58	(8.12 to 23.55)
COPD	9.54	(6.94 to 12.22)	23.64	(15.33 to 32.54)	23.36	(14.15 to 33.31)

[a] Reference level: 1. Influenza intensity: effect of influenza per 10% increase in influenza intensity; 2. Influenza epidemic: effect of influenza for influenza epidemic relative to epidemic baseline; 3. Influenza predominance: effect of influenza for influenza predominance relative to predominance baseline periods.

Table 12. Influenza Effects on Hospitalization: ER (%) in Three Measures of Influenza Activity Relative to the Corresponding Reference Levels[a] in the Current Week

Hospital Outcome / Age Group	Influenza Intensity		Influenza Epidemic		Influenza Predominance	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Cardiovascular						
All ages	1.74	(1.28 to 2.21)	4.65	(3.29 to 6.03)	5.57	(3.90 to 7.27)
65+	2.08	(1.42 to 2.75)	5.55	(3.72 to 7.41)	6.32	(4.09 to 8.60)
Stroke						
All ages	0.83	(0.00 to 1.68)	2.47	(0.09 to 4.90)	1.86	(−0.85 to 4.66)
Ischemic heart disease						
All ages	2.04	(1.05 to 3.04)	4.93	(2.14 to 7.79)	4.95	(1.72 to 8.28)
Respiratory						
All ages	2.56	(1.78 to 3.35)	6.58	(4.62 to 8.56)	6.21	(4.13 to 8.33)
65+	3.78	(2.98 to 4.58)	9.30	(6.92 to 11.73)	7.64	(5.14 to 10.19)
Acute respiratory disease						
All ages	12.20	(11.28 to 13.12)	39.37	(36.14 to 42.67)	35.76	(32.10 to 39.52)
0–14	3.37	(2.33 to 4.41)	8.63	(5.40 to 11.95)	7.80	(4.36 to 11.35)
Acute LRIs						
All ages	6.01	(4.65 to 7.38)	15.50	(11.75 to 19.37)	12.31	(8.43 to 16.33)
0–14	5.04	(3.06 to 7.06)	13.71	(8.19 to 19.50)	9.36	(3.68 to 15.35)
COPD						
All ages	2.58	(1.63 to 3.55)	10.33	(7.70 to 13.02)	8.91	(6.02 to 11.87)
65+	4.10	(3.10 to 5.11)	11.14	(8.12 to 14.25)	9.92	(6.71 to 13.22)
Asthma						
All ages	−1.75	(−3.10 to −0.38)	−1.55	(−5.41 to 2.47)	−1.81	(−6.08 to 2.65)
0–14	−4.27	(−6.15 to −2.36)	−6.91	(−12.07 to −1.44)	−6.69	(−12.43 to −0.56)

[a] Reference level: 1. Influenza intensity: effect of influenza per 10% change of influenza intensity; 2. Influenza epidemic: effect of influenza for influenza epidemic relative to epidemic baseline; 3. Influenza predominance: effect of influenza for influenza predominance relative to predominance baseline periods.

Table 13. Mean (SD) of Daily Air Pollutant Concentrations and Meteorologic Variables in Four Categories of Influenza Activity, During 1996–2002

	Influenza Epidemic[a]	Epidemic Baseline[b]	Influenza Predominance[c]	Predominance Baseline[d]
Days (*n*)	336	1602	238	888
Concentration ($\mu g/m^3$)				
NO_2 (24 hr)	62.5 (20.2)	60.0 (20.3)	66.4 (16.9)	64.0 (20.0)
SO_2 (24 hr)	16.7 (10.9)	17.6 (11.8)	15.8 (9.8)	16.1 (11.5)
PM_{10} (24 hr)	55.8 (28.8)	53.7 (25.0)	59.3 (25.5)	60.3 (24.7)
O_3 (8 hr)	31.4 (21.2)	40.1 (23.9)	33.7 (20.6)	43.9 (22.2)
Meteorologic variables				
Temperature (^oC)	19.5 (5.0)	24.1 (4.6)	17.4 (3.3)	22.4 (4.4)
RH (%)	79.2 (10.2)	76.4 (10.5)	78.2 (10.9)	73.6 (11.2)

[a] Weekly number of positive influenza isolates ≥ 4% of the annual total number of positive isolates for at least 2 consecutive weeks.

[b] Weekly number of positive influenza isolates < 2% of the annual total number of positive isolates for at least 2 consecutive weeks.

[c] Weekly number of positive influenza isolates ≥ 4% of the annual total number of positive isolates, and RSV isolates < 2% for at least 2 consecutive weeks.

[d] Weekly number of positive influenza isolates < 2% of the annual total number of positive isolates, and RSV isolates < 2% for at least 2 consecutive weeks.

Table 14. Mean (SD) of Daily Counts of Mortality in Four Categories of Influenza Activity, During 1996–2002

	Influenza Epidemic[a]	Epidemic Baseline[b]	Influenza Predominance[c]	Predominance Baseline[d]
All natural causes				
All ages	97.0 (13.6)	81.6 (118.0)	100.8 (12.0)	82.4 (12.9)
65+	76.9 (12.5)	63.0 (10.7)	80.7 (10.9)	63.5 (11.6)
Cardiovascular, all ages	29.7 (7.3)	22.8 (5.8)	31.8 (6.5)	23.2 (6.0)
Cardiac or heart disease, all ages	15.5 (4.6)	11.4 (3.8)	16.6 (4.4)	11.6 (3.9)
Stroke, all ages	10.6 (3.6)	8.6 (3.2)	11.2 (3.5)	8.7 (3.1)
Respiratory, all ages	21.2 (5.3)	15.1 (4.7)	21.5 (5.5)	15.2 (5.1)
LRI, all ages	11.9 (3.8)	8.8 (3.5)	11.7 (3.8)	8.9 (3.7)
COPD, all ages	8.2 (3.3)	5.3 (2.6)	8.6 (3.3)	5.3 (2.6)

[a] Weekly number of positive influenza isolates ≥ 4% of the annual total number of positive isolates for at least 2 consecutive weeks.

[b] Weekly number of positive influenza isolates < 2% of the annual total number of positive isolates for at least 2 consecutive weeks.

[c] Weekly number of positive influenza isolates ≥ 4% of the annual total number of positive isolates, and RSV isolates < 2% for at least 2 consecutive weeks.

[d] Weekly number of positive influenza isolates < 2% of the annual total number of positive isolates, and RSV isolates < 2% for at least 2 consecutive weeks.

Change in ER estimate without adjustment for influenza activity A 10-μg/m^3 increase in NO_2 concentration at lag 0–1 day was associated with an ER (%) estimate ranging from 1.03 (95% CI, 0.69 to 1.37) to 2.08 (95% CI, 1.10 to 3.07). The corresponding ER (%) estimates for SO_2, PM_{10}, and O_3 were from 0.54 (95% CI, −1.29 to 2.41) to 2.72 (95% CI, 1.22 to 4.23), from 0.40 (95% CI, −0.59 to 1.41) to 1.11 (95% CI, 0.27 to 1.95), and from 0.34 (95% CI, 0.02 to 0.66) to 0.94 (95% CI, −0.20 to 2.09), respectively (Tables 15 and 16).

Change in ER estimate with adjustment for influenza activity The following results were observed:

1. Influenza intensity: Influenza intensity was a confounder of the association between SO_2 and stroke and COPD, and between PM_{10} and cardiac or heart disease and COPD (compare Table 15 and Table 16 with Table 8).
2. Influenza epidemics: Epidemic was a confounder of the associations between NO_2 and stroke, LRI, and COPD. In addition, epidemic was a confounder of the association between SO_2 and COPD (compare Table 15 and Table 16 with Table 8).
3. Influenza predominance: Predominance was a confounder of the association between NO_2 and cardiac or heart disease, LRI, and COPD. In addition, predominance was a confounder of the associations between O_3 and cardiovascular disease, cardiac or heart disease, LRI, and COPD (compare Table 15 and Table 16 with Table 8).

Figures N.1–N.3 in Appendix N show the changes in ER estimates in all mortality outcomes per 10-μg/m^3 increase in concentration for lag 0–1 day, between models with and without adjustment for influenza activity. If the unadjusted and adjusted ER estimates lie on the diagonal line, it suggests that influenza activity is not a confounder of the association between pollutants and mortality outcomes.

Hospital Admissions

Influenza epidemic compared with baseline The mean daily admission was higher for all ages during influenza

Table 15. Confounding Effects of Influenza on Mortality: ER (%)[a] per 10-μg/m^3 Increase in Average Concentration of Pollutants at Lag 0–1 Day, With and Without Adjustments — Broad Categories of Cause of Death

Outcome / Pollutant	Without Adjustment		With Adjustment For: Influenza Intensity		Influenza Epidemic		Influenza Predominance	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
All Natural Causes, All Ages								
NO_2	1.03	(0.69 to 1.37)	1.06	(0.73 to 1.40)	1.01	(0.67 to 1.35)	1.01	(0.67 to 1.35)
SO_2	0.91	(0.40 to 1.42)	0.88	(0.37 to 1.39)	0.90	(0.39 to 1.41)	0.92	(0.41 to 1.43)
PM_{10}	0.51	(0.23 to 0.80)	0.58	(0.30 to 0.86)	0.51	(0.23 to 0.80)	0.54	(0.26 to 0.82)
O_3	0.34	(0.02 to 0.66)	0.36	(0.05 to 0.68)	0.35	(0.03 to 0.66)	0.29	(−0.02 to 0.61)
Cardiovascular, All Ages								
NO_2	1.38	(0.75 to 2.01)	1.38	(0.76 to 2.01)	1.32	(0.69 to 1.95)	1.30	(0.67 to 1.93)
SO_2	1.23	(0.27 to 2.21)	1.20	(0.24 to 2.17)	1.23	(0.26 to 2.20)	1.23	(0.26 to 2.20)
PM_{10}	0.63	(0.11 to 1.16)	0.72	(0.20 to 1.24)	0.62	(0.10 to 1.14)	0.64	(0.12 to 1.16)
O_3	0.63	(0.04 to 1.23)	0.62	(0.03 to 1.21)	0.60	(0.01 to 1.19)	**0.52**	**(−0.07 to 1.12)**
Respiratory, All Ages								
NO_2	1.41	(0.67 to 2.15)	1.42	(0.68 to 2.16)	1.34	(0.61 to 2.09)	1.35	(0.61 to 2.09)
SO_2	1.31	(0.21 to 2.43)	1.25	(0.14 to 2.37)	1.26	(0.15 to 2.39)	1.29	(0.18 to 2.41)
PM_{10}	0.69	(0.08 to 1.31)	0.78	(0.17 to 1.39)	0.68	(0.07 to 1.29)	0.72	(0.11 to 1.33)
O_3	0.36	(−0.33 to 1.05)	0.37	(−0.32 to 1.06)	0.36	(−0.33 to 1.05)	0.26	(−0.42 to 0.95)

[a] ER in bold if adjustment > |0.1%|.

Table 16. Confounding Effects of Influenza on Mortality: ER (%)[a] per 10-μg/m^3 Increase in Average Concentration of Pollutants at Lag 0–1 Day, With and Without Adjustments — Subcategories of Cause of Death

Outcome / Pollutant	Without Adjustment		With Adjustment For: Influenza Intensity		With Adjustment For: Influenza Epidemic		With Adjustment For: Influenza Predominance	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Stroke, All Ages								
NO_2	1.13	(0.19 to 2.08)	1.09	(0.14 to 2.04)	**1.02**	**(0.08 to 1.98)**	1.05	(0.10 to 2.00)
SO_2	1.08	(−0.36 to 2.53)	**0.97**	**(−0.47 to 2.44)**	1.00	(−0.44 to 2.46)	1.02	(−0.42 to 2.49)
PM_{10}	0.81	(0.03 to 1.60)	0.85	(0.07 to 1.64)	0.77	(−0.01 to 1.56)	0.80	(0.02 to 1.59)
O_3	0.54	(−0.35 to 1.43)	0.52	(−0.37 to 1.41)	0.50	(−0.39 to 1.40)	0.46	(−0.43 to 1.36)
Cardiac or Heart Disease, All Ages								
NO_2	2.08	(1.10 to 3.07)	2.09	(1.12 to 3.07)	1.98	(1.00 to 2.97)	**1.97**	**(0.99 to 2.95)**
SO_2	2.72	(1.22 to 4.23)	2.65	(1.16 to 4.17)	2.70	(1.21 to 4.22)	2.74	(1.24 to 4.25)
PM_{10}	0.96	(0.15 to 1.78)	**1.10**	**(0.29 to 1.91)**	0.94	(0.13 to 1.75)	0.99	(0.18 to 1.81)
O_3	0.61	(−0.32 to 1.54)	0.59	(−0.33 to 1.51)	0.56	(−0.37 to 1.49)	**0.43**	**(−0.49 to 1.35)**
LRI, All Ages								
NO_2	1.75	(0.74 to 2.77)	1.73	(0.72 to 2.74)	**1.64**	**(0.63 to 2.65)**	**1.62**	**(0.61 to 2.63)**
SO_2	2.21	(0.71 to 3.73)	2.13	(0.62 to 3.66)	2.11	(0.60 to 3.63)	2.11	(0.60 to 3.64)
PM_{10}	1.11	(0.27 to 1.95)	1.16	(0.33 to 2.00)	1.07	(0.24 to 1.90)	1.09	(0.26 to 1.93)
O_3	0.41	(−0.52 to 1.35)	0.41	(−0.52 to 1.35)	0.41	(−0.52 to 1.34)	**0.30**	**(−0.62 to 1.24)**
COPD, All Ages								
NO_2	1.39	(0.18 to 2.61)	1.30	(0.10 to 2.51)	**1.17**	**(−0.04 to 2.39)**	**1.22**	**(0.01 to 2.44)**
SO_2	0.54	(−1.29 to 2.41)	**0.30**	**(−1.53 to 2.17)**	**0.37**	**(−1.46 to 2.24)**	0.47	(−1.37 to 2.35)
PM_{10}	0.40	(−0.59 to 1.41)	**0.52**	**(−0.46 to 1.52)**	0.34	(−0.65 to 1.34)	0.44	(−0.55 to 1.45)
O_3	0.94	(−0.20 to 2.09)	0.90	(−0.23 to 2.05)	0.88	(−0.26 to 2.03)	**0.72**	**(−0.42 to 1.87)**

[a] ER in bold if adjustment > |0.1%|.

Table 17. Mean (SD) of Daily Counts of Hospitalizations in Four Categories of Influenza Activity, During 1996–2002

Hospitalization Outcome	Influenza Epidemic[a]	Epidemic Baseline[b]	Influenza Predominance[c]	Predominance Baseline[d]
Cardiovascular, all ages	209.8 (48.9)	200.0 (46.5)	220.2 (47.5)	200.9 (48.1)
Stroke, all ages	47.8 (10.0)	46.3 (9.6)	49.9 (9.9)	46.7 (10.1)
IHD, all ages	46.4 (12.4)	45.9 (12.9)	48.2 (12.5)	46.0 (13.3)
Respiratory, all ages	334.6 (67.0)	250.3 (43.6)	346.5 (68.3)	240.7 (42.0)
ARD, all ages	140.9 (35.4)	94.3 (22.9)	140.9 (39.0)	85.4 (18.1)
Acute LRI, all ages	64.3 (16.7)	41.6 (12.3)	64.3 (18.0)	37.9 (10.1)
COPD, all ages	107.9 (22.0)	87.8 (18.6)	113.8 (20.9)	90.0 (18.7)
Asthma, all ages	28.3 (8.3)	27.4 (9.0)	29.4 (8.9)	29.6 (9.6)

[a] Weekly number of positive influenza isolates ≥ 4% of the annual total number of positive isolates for at least 2 consecutive weeks.

[b] Weekly number of positive influenza isolates < 2% of the annual total number of positive isolates for at least 2 consecutive weeks.

[c] Weekly number of positive influenza isolates ≥ 4% of the annual total number of positive isolates, and RSV isolates < 2% for at least 2 consecutive weeks.

[d] Weekly number of positive influenza isolates < 2% of the annual total number of positive isolates, and RSV isolates < 2% for at least 2 consecutive weeks.

epidemics for each of the discharge diagnoses compared with the baseline periods (Table 17).

Influenza predominance compared with baseline The mean daily admission was higher for all ages during influenza predominance for each of the discharge diagnoses compared with the baseline periods (Table 17).

Change in ER estimate without adjustment for influenza activity The ER estimates for the four pollutants were positive for all admission diagnoses, except for the associations between SO_2 and stroke and asthma and the association between O_3 and stroke. The ER (%) estimates per 10-μg/m^3 increase in concentration of NO_2 in lag 0–1 day ranged from 0.33 (95% CI, −0.09 to 0.76) to 1.94 (95% CI, 1.55 to 2.33). The corresponding estimates for SO_2, PM_{10}, and O_3 were from −0.17 (95% CI, −0.80 to 0.47) to 0.98 (95% CI, 0.57 to 1.39), from 0.12 (95% CI, −0.23 to 0.48) to 1.32 (95% CI, 0.99 to 1.65), and from −0.05 (95% CI, −0.43 to 0.33) to 1.55 (95% CI, 1.11 to 1.99), respectively (Tables 18 and 19).

Change in ER estimate with adjustment for influenza activity The following results were observed:

1. *Influenza intensity:* Intensity was a confounder of the association between the three gaseous pollutants and ARD admissions. In addition, intensity was a confounder of the association between PM_{10} and ALRI (compare Tables 18 and 19 with Table 9).
2. *Influenza epidemic:* Epidemic was a confounder of the association between each of the four pollutants and ARD admissions (compare Tables 18 and 19 with Table 9).
3. *Influenza predominance:* Predominance was a confounder of the association between each of the four pollutants and ARD admissions (compare Tables 18 and 19 with Table 9).

Figures O.1–O.3 in Appendix O show the ER estimates in all admission outcomes per 10-μg/m^3 change in the concentration at lag 0–1 day, with and without adjustment for influenza activity. Again, if the unadjusted and adjusted ER estimates lie on the diagonal line, it suggests that influenza activity is not a confounder of the association between pollutants and hospital admissions.

Table 18. Confounding Effects of Influenza on Hospitalization: ER (%)[a] per 10-μg/m^3 Increase in Average Concentration of Pollutants at Lag 0–1 Day, With and Without Adjustments — Cardiovascular Diseases

Outcome / Pollutant	Without Adjustment		With Adjustment For: Influenza Intensity		With Adjustment For: Influenza Epidemic		With Adjustment For: Influenza Predominance	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Cardiovascular, All Ages								
NO_2	1.00	(0.73 to 1.26)	1.02	(0.76 to 1.28)	0.97	(0.70 to 1.23)	0.96	(0.69 to 1.22)
SO_2	0.98	(0.57 to 1.39)	0.96	(0.56 to 1.37)	0.98	(0.57 to 1.38)	0.96	(0.55 to 1.36)
PM_{10}	0.58	(0.36 to 0.80)	0.62	(0.39 to 0.84)	0.55	(0.33 to 0.77)	0.56	(0.34 to 0.78)
O_3	0.12	(−0.12 to 0.37)	0.15	(−0.09 to 0.40)	0.10	(−0.15 to 0.35)	0.07	(−0.18 to 0.31)
Stroke, All Ages								
NO_2	0.33	(−0.09 to 0.76)	0.32	(−0.10 to 0.75)	0.29	(−0.14 to 0.72)	0.33	(−0.10 to 0.76)
SO_2	−0.17	(−0.80 to 0.47)	−0.22	(−0.86 to 0.42)	−0.19	(−0.82 to 0.46)	−0.15	(−0.79 to 0.50)
PM_{10}	0.12	(−0.23 to 0.48)	0.12	(−0.24 to 0.48)	0.09	(−0.27 to 0.45)	0.13	(−0.23 to 0.49)
O_3	−0.05	(−0.43 to 0.33)	−0.04	(−0.42 to 0.34)	−0.10	(−0.48 to 0.28)	−0.11	(−0.49 to 0.27)
IHD, All Ages								
NO_2	0.94	(0.46 to 1.42)	0.96	(0.48 to 1.44)	0.94	(0.46 to 1.43)	0.96	(0.47 to 1.45)
SO_2	0.93	(0.21 to 1.66)	0.93	(0.21 to 1.66)	1.01	(0.28 to 1.74)	1.02	(0.29 to 1.75)
PM_{10}	0.72	(0.32 to 1.13)	0.75	(0.35 to 1.16)	0.73	(0.33 to 1.14)	0.76	(0.35 to 1.16)
O_3	0.26	(−0.17 to 0.69)	0.27	(−0.16 to 0.70)	0.22	(−0.22 to 0.65)	0.20	(−0.24 to 0.63)

[a] ER in bold if adjustment > |0.1%|.

Table 19. Confounding Effects of Influenza on Hospitalization: ER (%)[a] per 10-μg/m^3 Increase in Average Concentration of Pollutants at Lag 0–1 Day, With and Without Adjustments — Respiratory Diseases

Outcome / Pollutant	Without Adjustment		With Adjustment For: Influenza Intensity		With Adjustment For: Influenza Epidemic		With Adjustment For: Influenza Predominance	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Respiratory, All Ages								
NO_2	0.75	(0.50 to 1.00)	0.76	(0.52 to 1.01)	0.75	(0.50 to 1.00)	0.75	(0.50 to 1.00)
SO_2	0.13	(−0.24 to 0.50)	0.07	(−0.29 to 0.44)	0.14	(−0.23 to 0.50)	0.15	(−0.22 to 0.52)
PM_{10}	0.60	(0.40 to 0.80)	0.61	(0.40 to 0.81)	0.57	(0.37 to 0.77)	0.60	(0.39 to 0.80)
O_3	0.81	(0.58 to 1.04)	0.80	(0.58 to 1.03)	0.78	(0.55 to 1.00)	0.74	(0.52 to 0.97)
ARD, All Ages								
NO_2	1.22	(0.74 to 1.71)	**0.90**	**(0.47 to 1.32)**	**0.82**	**(0.40 to 1.25)**	**0.71**	**(0.26 to 1.15)**
SO_2	0.55	(−0.18 to 1.29)	**0.11**	**(−0.53 to 0.75)**	**0.25**	**(−0.38 to 0.89)**	**0.28**	**(−0.39 to 0.95)**
PM_{10}	0.88	(0.49 to 1.28)	0.85	(0.50 to 1.20)	**0.65**	**(0.30 to 1.00)**	**0.68**	**(0.31 to 1.04)**
O_3	1.55	(1.11 to 1.99)	**1.25**	**(0.86 to 1.63)**	**1.14**	**(0.76 to 1.53)**	**0.94**	**(0.54 to 1.35)**
ALRI, All Ages								
NO_2	0.76	(0.27 to 1.24)	0.78	(0.30 to 1.27)	0.75	(0.27 to 1.24)	0.67	(0.18 to 1.16)
SO_2	0.09	(−0.64 to 0.83)	0.00	(−0.72 to 0.73)	0.02	(−0.70 to 0.75)	0.01	(−0.72 to 0.75)
PM_{10}	0.66	(0.26 to 1.05)	**0.77**	**(0.38 to 1.17)**	0.70	(0.31 to 1.09)	0.67	(0.28 to 1.07)
O_3	1.09	(0.64 to 1.54)	1.18	(0.74 to 1.63)	1.18	(0.73 to 1.63)	1.03	(0.58 to 1.48)
COPD, All Ages								
NO_2	1.94	(1.55 to 2.33)	1.92	(1.53 to 2.32)	1.86	(1.47 to 2.25)	1.92	(1.53 to 2.31)
SO_2	0.70	(0.10 to 1.31)	0.62	(0.01 to 1.22)	0.62	(0.02 to 1.22)	0.70	(0.10 to 1.31)
PM_{10}	1.32	(0.99 to 1.65)	1.33	(1.01 to 1.66)	1.28	(0.96 to 1.61)	1.35	(1.03 to 1.68)
O_3	1.54	(1.17 to 1.92)	1.54	(1.16 to 1.91)	1.50	(1.14 to 1.88)	1.47	(1.09 to 1.84)
Asthma, All Ages								
NO_2	0.96	(0.31 to 1.62)	1.04	(0.38 to 1.70)	0.95	(0.29 to 1.61)	1.05	(0.39 to 1.72)
SO_2	−0.28	(−1.28 to 0.74)	−0.19	(−1.20 to 0.83)	−0.30	(−1.31 to 0.73)	−0.22	(−1.23 to 0.81)
PM_{10}	0.81	(0.27 to 1.36)	0.83	(0.28 to 1.37)	0.82	(0.27 to 1.36)	0.87	(0.32 to 1.42)
O_3	1.53	(0.91 to 2.16)	1.56	(0.94 to 2.18)	1.55	(0.93 to 2.17)	1.58	(0.96 to 2.21)

[a] ER in bold if adjustment > |0.1%|.

MODIFYING EFFECTS OF INFLUENZA ON HEALTH EFFECTS OF AIR POLLUTION

Mortality

The baseline effects of the air pollutants on mortality, which were calculated under the assumption of zero influenza intensity, were statistically significant for CVD when associated with NO_2 and SO_2, and for RD when associated with NO_2 (with positive changes in ER [%]: 1.23, 1.64, and 1.24, respectively), but were not statistically significant for all mortality outcomes associated with O_3 (see Table 20 for CIs). Statistically significant modifying effects of influenza were found for the effects of O_3 on mortality for RD and COPD (with increases in ER [%] of 0.59 and 1.05, respectively), but not for the other pollutants.

Hospitalization

The effects of NO_2 on hospitalization at the baseline level of influenza were statistically significant for all the health outcomes under study (except for ARD), with ER (%) ranging from 0.85 to 1.84 (see Table 21 for CIs). Statistically significant modifying effects of influenza were found for the effects of NO_2 on hospitalization for COPD in the 65+ age group (with an increase in ER [%] of 0.43).

There were statistically significant effects of SO_2 on hospitalization for CVD at the baseline level of influenza (ER [%] of 1.10 and 1.50 for the all-ages and 65+ age groups, respectively). The modifying effects of influenza for the effect of SO_2 on hospitalization were found to be statistically significant only for ARD in the all-ages group, with an increase in ER (%) of 0.86 (see Table 21 for CIs).

For PM_{10}, statistically significant effects at the baseline level of influenza were found for all the health outcomes under study, ranging from 0.55 to 1.49 (see Table 22 for CIs). No statistically significant modifying effect of influenza was found for PM_{10} on hospitalization in all the categories under study.

The effects of O_3 at the baseline level of influenza for health outcomes were found to be statistically significant for all RD groups under study (ER [%] ranging from 0.53 to

Table 20. Modifying Effects of Influenza for Air Pollution Effect on Mortality: ER (%) per 10-μg/m^3 Increase in Average Concentration of Pollutant at Lag 0–1 Day for Modifying Effect,[a] Baseline Effect,[b] and Effect at Mean Level of Influenza Intensity[c]

Pollutant / Disease	Modifying Effect		Baseline Effect		Effect at Mean Level of Influenza Intensity	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
NO_2						
RD	0.18	(−0.45 to 0.82)	1.24	(0.27 to 2.22)	1.42	(0.45 to 2.41)
COPD	1.01	(−0.03 to 2.05)	0.26	(−1.34 to 1.87)	1.26	(−0.33 to 2.89)
CVD	0.15	(−0.39 to 0.70)	1.23	(0.41 to 2.06)	1.39	(0.56 to 2.22)
SO_2						
RD	0.05	(−1.12 to 1.23)	1.20	(−0.38 to 2.81)	1.25	(−0.35 to 2.88)
COPD	0.32	(−1.58 to 2.27)	−0.03	(−2.67 to 2.69)	0.30	(−2.35 to 3.01)
CVD	−0.45	(−1.45 to 0.55)	1.64	(0.27 to 3.02)	1.18	(−0.20 to 2.57)
PM_{10}						
RD	0.08	(−0.39 to 0.55)	0.69	(−0.10 to 1.49)	0.77	(−0.01 to 1.56)
COPD	0.50	(−0.26 to 1.27)	−0.05	(−1.36 to 1.28)	0.45	(−0.83 to 1.75)
CVD	0.25	(−0.15 to 0.65)	0.45	(−0.23 to 1.13)	0.70	(0.03 to 1.37)
O_3						
RD	0.59	(0.04 to 1.14)	−0.16	(−1.00 to 0.69)	0.42	(−0.44 to 1.29)
COPD	1.05	(0.17 to 1.93)	−0.11	(−1.51 to 1.32)	0.94	(−0.49 to 2.38)
CVD	0.04	(−0.42 to 0.51)	0.58	(−0.15 to 1.31)	0.62	(−0.12 to 1.36)

[a] Modifying effect is the change in ER when influenza intensity increases to 10%.

[b] Baseline effect is when the influenza intensity is assumed equal to 0.

[c] Effect at mean level of influenza intensity is when influenza intensity is assumed equal to 10%.

Table 21. Modifying Effects of Influenza for NO_2 and SO_2 Effects on Hospitalization: ER (%) per 10-μg/m^3 Increase in Average Concentration of Pollutant at Lag 0–1 Day for Modifying Effect,[a] Baseline Effect,[b] and Effect at Mean Level of Influenza Intensity[c]

Pollutant / Outcome, Age	Modifying Effect		Baseline Effect		Effect at Mean Level of Influenza Intensity	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
NO_2						
RD						
All ages	−0.09	(−0.32 to 0.15)	0.85	(0.51 to 1.18)	0.76	(0.51 to 1.01)
65+	−0.07	(−0.35 to 0.22)	1.06	(0.64 to 1.48)	0.99	(0.68 to 1.30)
ARD						
All ages	0.33	(−0.03 to 0.70)	0.55	(−0.02 to 1.12)	0.88	(0.46 to 1.31)
0–14	−0.18	(−0.57 to 0.22)	0.44	(−0.16 to 1.04)	0.26	(−0.19 to 0.71)
COPD						
All ages	0.09	(−0.26 to 0.44)	1.84	(1.32 to 2.35)	1.93	(1.54 to 2.32)
65+	0.43	(0.05 to 0.81)	1.19	(0.62 to 1.76)	1.62	(1.19 to 2.06)
CVD						
All ages	0.04	(−0.20 to 0.28)	0.98	(0.63 to 1.33)	1.02	(0.76 to 1.29)
65+	−0.03	(−0.32 to 0.26)	1.30	(0.89 to 1.70)	1.27	(0.96 to 1.57)
SO_2						
RD						
All ages	−0.24	(−0.65 to 0.16)	0.31	(−0.23 to 0.86)	0.07	(−0.30 to 0.44)
65+	−0.33	(−0.83 to 0.17)	0.37	(−0.30 to 1.05)	0.04	(−0.42 to 0.50)
ARD						
All ages	0.86	(0.20 to 1.53)	−0.77	(−1.69 to 0.16)	0.09	(−0.55 to 0.73)
0–14	0.53	(−0.16 to 1.22)	−0.60	(−1.56 to 0.37)	−0.07	(−0.74 to 0.60)
COPD						
All ages	0.35	(−0.32 to 1.02)	0.29	(−0.57 to 1.16)	0.64	(0.04 to 1.25)
65+	0.41	(−0.29 to 1.13)	0.17	(−0.77 to 1.12)	0.58	(−0.07 to 1.24)
CVD						
All ages	−0.15	(−0.60 to 0.30)	1.10	(0.52 to 1.69)	0.95	(0.54 to 1.36)
65+	−0.28	(−0.80 to 0.25)	1.50	(0.83 to 2.17)	1.22	(0.75 to 1.69)

[a] Modifying effect is the change in ER when influenza intensity increases to 10%.

[b] Baseline effect is when the influenza intensity is assumed equal to 0.

[c] Effect at mean level of influenza intensity is when influenza intensity is assumed equal to 10%.

Table 22. Modifying Effects of Influenza for PM_{10} and O_3 Effects on Hospitalization: ER (%) per 10-μg/m^3 Increase in Average Concentration of Pollutant at Lag 0–1 Day for Modifying Effect,[a] Baseline Effect,[b] and Effect at Mean Level of Influenza Intensity[c]

Pollutant / Outcome, Age	Modifying Effect		Baseline Effect		Effect at Mean Level of Influenza Intensity	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
PM_{10}						
RD						
All ages	−0.16	(−0.34 to 0.01)	0.78	(0.51 to 1.06)	0.62	(0.41 to 0.82)
65+	−0.15	(−0.36 to 0.06)	0.98	(0.64 to 1.32)	0.82	(0.57 to 1.08)
ARD						
All ages	0.13	(−0.14 to 0.40)	0.70	(0.24 to 1.16)	0.83	(0.48 to 1.18)
0–14	−0.11	(−0.40 to 0.19)	0.55	(0.06 to 1.03)	0.44	(0.08 to 0.81)
COPD						
All ages	−0.14	(−0.40 to 0.12)	1.49	(1.06 to 1.92)	1.34	(1.02 to 1.67)
65+	0.09	(−0.19 to 0.37)	1.02	(0.55 to 1.49)	1.11	(0.75 to 1.47)
CVD						
All ages	−0.02	(−0.20 to 0.16)	0.64	(0.35 to 0.93)	0.62	(0.40 to 0.84)
65+	−0.12	(−0.33 to 0.09)	0.90	(0.57 to 1.23)	0.78	(0.53 to 1.03)
O_3						
RD						
All ages	0.24	(0.04 to 0.43)	0.60	(0.32 to 0.88)	0.84	(0.61 to 1.06)
65+	0.40	(0.16 to 0.64)	0.53	(0.17 to 0.89)	0.93	(0.64 to 1.22)
ARD						
All ages	0.46	(0.15 to 0.76)	0.84	(0.37 to 1.31)	1.30	(0.91 to 1.68)
0–14	−0.19	(−0.51 to 0.13)	0.94	(0.43 to 1.45)	0.75	(0.34 to 1.16)
COPD						
All ages	0.17	(−0.14 to 0.48)	1.39	(0.93 to 1.85)	1.56	(1.18 to 1.93)
65+	0.40	(0.07 to 0.73)	0.70	(0.19 to 1.20)	1.10	(0.69 to 1.52)
CVD						
All ages	0.20	(−0.02 to 0.41)	0.00	(−0.29 to 0.30)	0.20	(−0.05 to 0.45)
65+	0.21	(−0.03 to 0.46)	−0.03	(−0.37 to 0.31)	0.18	(−0.11 to 0.47)

[a] Modifying effect is the change in ER when influenza intensity increases to 10%.

[b] Baseline effect is when the influenza intensity is assumed equal to 0.

[c] Effect at mean level of influenza intensity is when influenza intensity is assumed equal to 10%.

1.39), but not for CVD. The changes in ER of hospitalization associated with O_3 for RD were statistically significant. The ER (%) increased 0.24 and 0.40 for RD in the all-age and 65+ age groups, respectively; increased 0.46 for ARD in the all-age group; and increased 0.40 for COPD in the 65+ group when influenza intensity increased from 0 to 10% (see Table 22 for CIs).

In analyses stratified by males (M) and females (F) (data not shown), we found statistically significant effect modification of influenza (shown as change in ER [%]; 95% CI) for the effects of O_3 on hospitalization for the following groups: for RD in M (0.38; 0.08 to 0.69) and F (0.48; 0.15 to 0.82) for the 65+ age group; and for COPD in F for the all-ages (0.63; 0.19 to 1.07) and 65+ (0.88; 0.36 to 1.40) groups. The effect modification of influenza on the effects of the other pollutants on hospitalization was not consistently significant, but did show statistically significant positive changes in the ER of NO_2 on COPD in M for the 65+ age group (0.47; 0.01 to 0.94), statistically significant negative changes in the ER of PM_{10} on RD in M for all ages (−0.31; −0.51 to −0.11) (data not shown).

EFFECTS OF AIR POLLUTION IN SOCIALLY DEPRIVED URBAN AREAS

Figure 9 shows the social deprivation level by geographic area in the whole city of Hong Kong, excluding suburban areas. Most of the areas of high social deprivation were in the northern territories bordering mainland China and in the outer islands. There were also a few highly deprived areas in the inner city.

There were on average 19, 36, and 17 deaths per day from all natural causes in the urban areas with low, middle, and

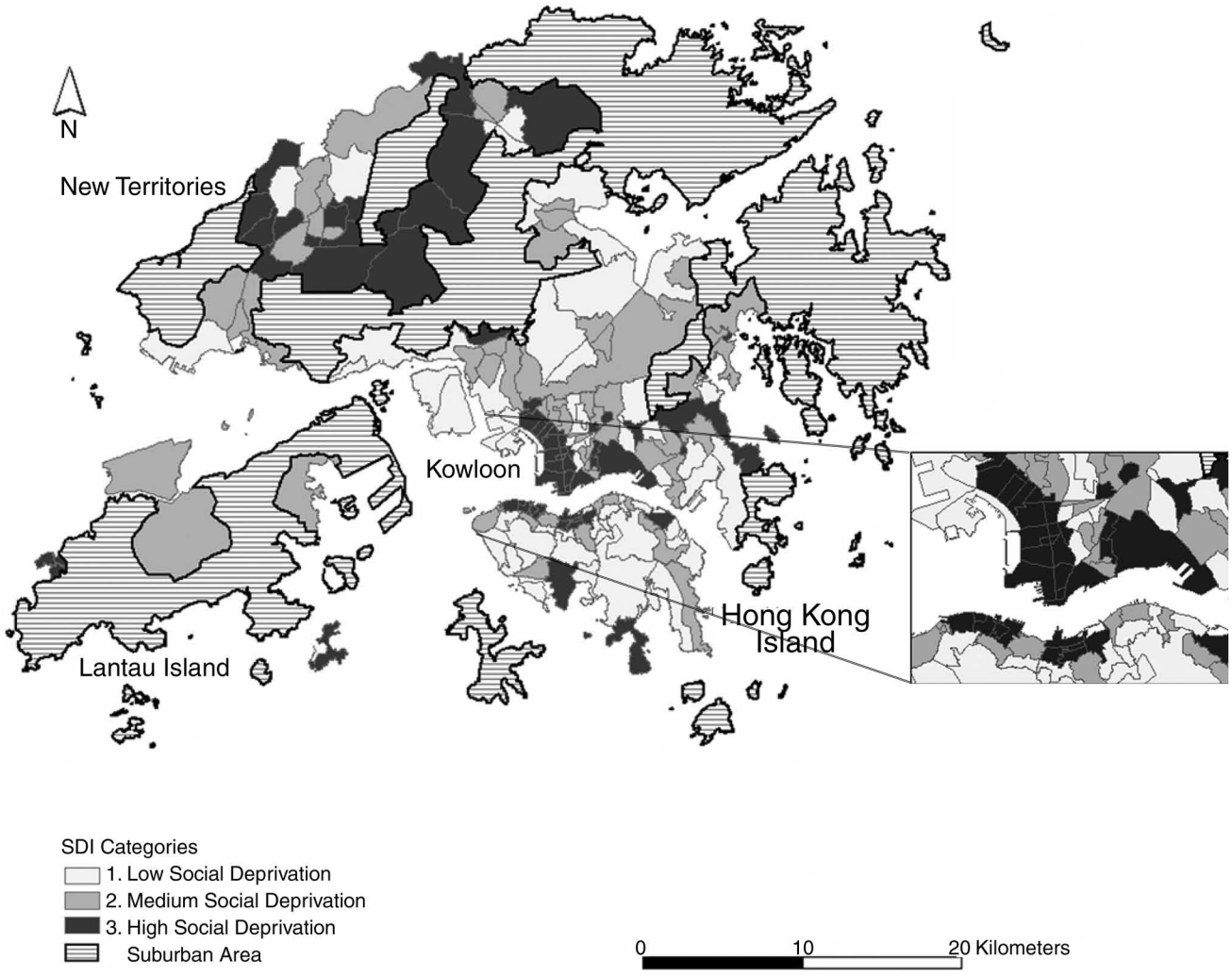

Figure 9. Map of Hong Kong showing three levels of SDI in 2001. Suburban areas are shown but not included in the SDI.

high SDI levels, respectively. The corresponding average daily counts for hospitalization were 30, 46, and 27 for CVD, and 39, 59, and 34 for RD, showing a U-shaped distribution because of a higher population in the middle SDI group. However, in terms of rates per population, increasing mortality and hospitalizations were associated with higher social deprivation (Appendix G).

Effects of Air Pollution by Stratification of Each SDI Group

For all natural causes of mortality and the subcategory of cardiovascular causes, the biggest single-day effects for all air pollutants occurred at either lag 0 or lag 1 day (Tables K.1. and K.2 in Appendix K). These lag patterns of ER were comparable in the high, middle, and low SDI groups (see the tables in Appendices P and Q). With the pollutant concentration at lag 0–1 day, the point estimates of ER associated with NO_2 and SO_2 for all natural causes of mortality and the subcategory of cardiovascular causes were higher in the middle SDI group than in the low SDI group, except with SO_2 for cardiovascular mortality (Figure 10). They were the highest in the high SDI group, except NO_2 for all natural mortality. With concentration measured at lag 0–1 day, for O_3, the point estimates of ER were higher in the middle SDI group than in the low and high SDI groups. However, there was no clear pattern for PM_{10} effects (Figure 10).

For respiratory mortality at lag 0–1 day, the point estimates of ER for NO_2 and SO_2 increased from the low to high SDI groups (Figure 10), with ER (%) increasing from 0.76 to 1.44 for NO_2, and from 0.90 to 2.27 for SO_2. However, for PM_{10} and O_3, the point estimates of ER (%) varied

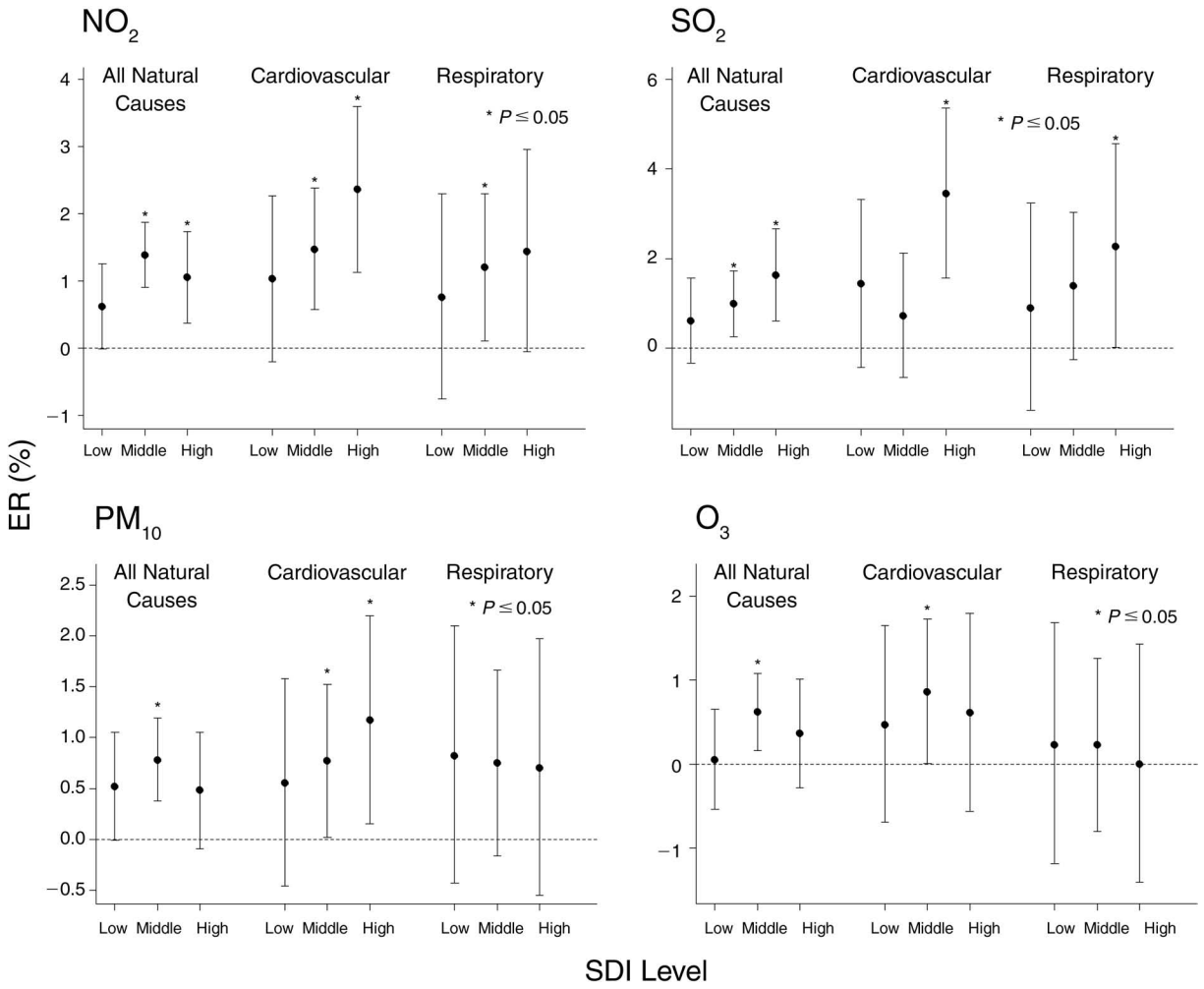

Figure 10. Excess risk of mortality for all natural, cardiovascular-related, and respiratory-related causes by three levels (low, middle, and high) of social deprivation at lag 0–1 day per 10-μg/m^3 increase in NO_2, SO_2, PM_{10}, and O_3 concentration.

Table 23. Difference in ER (%) of Mortality Associated with Air Pollution per 10-μg/m^3 Increase in Average Concentration of Pollutant Between Areas with Different SDI Levels at Lag 0–1 Day

SDI Level / Pollutant	All Natural Causes		Respiratory		Cardiovascular	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
High vs. Middle						
NO_2	0.45	(−0.16 to 1.06)	1.03	(−0.11 to 2.18)	0.94	(−0.41 to 2.31)
SO_2	1.15	(0.06 to 2.26)	2.74	(0.66 to 4.85)	1.62	(−0.83 to 4.12)
PM_{10}	0.23	(−0.25 to 0.72)	0.49	(−0.40 to 1.40)	0.49	(−0.58 to 1.58)
O_3	0.14	(−0.41 to 0.70)	0.09	(−0.95 to 1.14)	0.75	(−0.50 to 2.01)
High vs. Low						
NO_2	0.51	(−0.18 to 1.20)	1.35	(0.49 to 2.67)	0.59	(−0.98 to 2.18)
SO_2	1.38	(0.13 to 2.63)	2.16	(−0.19 to 4.57)	2.42	(−0.47 to 5.38)
PM_{10}	0.12	(−0.42 to 0.67)	0.82	(−0.20 to 1.86)	−0.15	(−1.39 to 1.10)
O_3	0.14	(−0.48 to 0.76)	0.13	(−1.06 to 1.33)	0.33	(−1.12 to 1.79)
Trend Test						
NO_2	0.16	(−0.07 to 0.39)	0.45	(0.01 to 0.88)	0.21	(−0.32 to 0.73)
SO_2	0.45	(0.03 to 0.87)	0.71	(−0.08 to 1.51)	0.81	(−0.15 to 1.71)
PM_{10}	0.04	(−0.15 to 0.22)	0.27	(−0.07 to 0.61)	−0.04	(−0.46 to 0.37)
O_3	0.05	(−0.16 to 0.25)	0.04	(−0.35 to 0.44)	0.12	(−0.37 to 0.60)

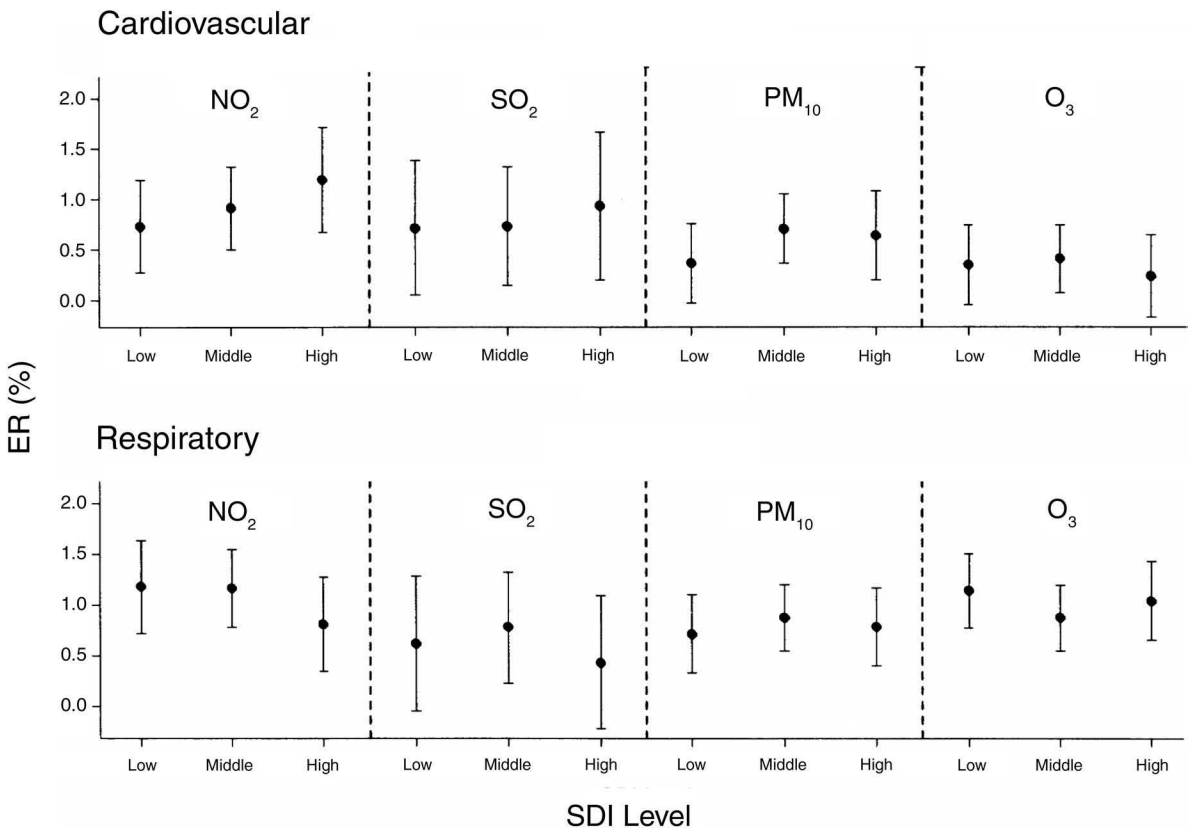

Figure 11. ER of cardiovascular and respiratory hospitalizations per 10-μg/m^3 increase in pollutant concentration (NO_2, SO_2, PM_{10}, and O_3) by three levels of SDI (low, middle, and high) at lag 0–1 day.

from low to high SDI groups by only a small magnitude (0.82 to 0.70 for PM_{10}; 0.23 to 0.0 for O_3).

Differences in the Effects of Air Pollution Among SDI Groups

For mortality due to all natural causes and cardiovascular causes, the ER associated with SO_2 at the lag 0–1 day increased, with a significant trend seen from low to middle to high SDI group. However, the effects of PM_{10} and O_3 did not vary much with SDI levels (Table 23). The trend and magnitude of the differences between SDI groups in the effects of all pollutants on respiratory mortality were similar in direction to those of all natural mortality but were not statistically significant (see Table 23 for CIs).

For cardiovascular and respiratory hospitalizations, most of the ERs were statistically significant in each SDI group, but there were no clear patterns to indicate that residents in higher social deprivation areas were at higher or lower risk of hospitalization (Figure 11). The ER of hospitalization associated with air pollution was also not related to any of six socioeconomic characteristics (proportion of residents with a household income < U.S. $250 per month; no schooling at all; one-person household; never-married status; and subtenancy [data not shown]).

DISCUSSION

INFLUENZA-ASSOCIATED MORTALITY AND HOSPITAL ADMISSIONS

In Hong Kong, C. M. Wong and associates (2004, 2006) have shown in Poisson regression models that influenza intensity was strongly associated with both mortality and hospitalization for cardio-respiratory diseases, in all age groups. Li and colleagues (2006) also showed statistically significant associations between influenza intensity and both mortality and hospitalization using the correlation coefficients in monthly data. Employing generalized additive modeling in the daily time-series method, we reconfirmed that influenza is associated with both cardio-respiratory mortality and hospitalization in all age groups in Hong Kong. Our estimates of ER (%) per 10% change in influenza intensity in cardiovascular and respiratory mortality in the all-ages group are 5.1 and 4.8, respectively (Table 11); these data are compatible with those from Hong Kong published previously, which showed an ER (%) of approximately 5.5 (Wong CM et al. 2004). For COPD in the all-ages group, the estimates of association of mortality with influenza intensity in both studies are also similar. For the hospitalization outcomes, our estimates of ER (%) per 10% change in influenza intensity for ALRI in the 0–14 and all-ages groups were 6.0 and 5.0, respectively, which are lower than the estimates (14.7 and 11.6, respectively) for the same outcomes published in the study by C. M. Wong and colleagues (2006). These lower hospitalization estimates in our study may be related to our modeling daily rather than weekly series, and controlling for more residual variations.

In this study, we cannot compare the ERs assessed by the three measures of influenza activity directly because they use different baseline levels. However, we can compare their statistical significance. Except for asthma and stroke in the all-ages group for hospitalization, all three measures of influenza activity showed consistently statistically significant results for both the CVD and RD categories. This analysis is limited, however, because of its use of virology data only from QMH, which accounts for about 40% of the total specimens in Hong Kong. Fortunately, in Hong Kong, representative virology surveillance data from 1998 were available from the DH. We calculated the Spearman correlation between the data we used from the QMH and those from the DH for the period 1998–2002 and found that they are highly correlated (correlation coefficient, 0.8). Furthermore, the data from the QMH accounted for about 40% of the total microbiology surveillance data from the DH, and influenza activity was found to be highly synchronized across geographic regions, as observed through a wavelet analysis (data not shown). We therefore believe that the data we used from the QMH are representative of the whole territory of Hong Kong.

CONFOUNDING EFFECTS OF INFLUENZA ACTIVITY

One of the aims of the present investigation was to assess the extent to which influenza activity confounds possible associations between short-term effects of air pollution and daily mortality and hospital admissions. In our study, influenza epidemics were identified by three virologically defined measures of influenza activity, in contrast to previous studies, which identified epidemics based on either emergency hospital admissions for influenza or respiratory mortality counts (Katsouyanni et al. 1996, 2001; Schwartz et al. 1996; Vigotti et al. 1996; Zmirou et al. 1998; Sunyer et al. 2000). We found that, after controlling for influenza activity, the ER (%) estimate for PM_{10} ranged from 0.51 to 0.67 for mortality due to all natural causes and 0.62 to 0.72 for mortality due to cardiovascular-related causes for a 10-$\mu g/m^3$ increase in PM_{10} concentrations (Table 15).

These findings are similar to those reported by Touloumi and associates (2005), who assessed the association between PM_{10} and mortality outcomes using ten approaches to control for influenza, including excess event counts and

virology monitoring. They concluded that influenza epidemics did not confound the associations between PM_{10} concentration and all natural and cardiovascular mortality. Similarly, Braga and coworkers (2000) assessed whether respiratory epidemics confounded the association between PM_{10} concentrations and daily mortality in five U.S. cities using data on pneumonia-related hospital admissions as an indicator for influenza. They showed that the PM_{10} effect was slightly reduced after adjusting for influenza, suggesting that the association between air pollution and daily mortality was robust enough to support the conclusion that there was no confounding.

Tobias and Campbell (1999) reported that, although controlling for influenza cases resulted in a 10% decrease in the effect of exposure to black smoke on total mortality, exposure to black smoke remained significant. Another study (Tobias et al. 1999) assessing the association between black smoke and asthma emergency admissions showed that, compared with modeling epidemics using a single dummy variable, adjusting for multiple dummy variables for different epidemics resulted in increased air pollution coefficients. On the other hand, compared with no adjustment for influenza epidemics, adjusting for epidemics decreased the regression coefficients for exposure to black smoke and SO_2 and increased the regression coefficients for exposure to NO_2 and O_3.

We have provided a simple flow chart showing our assumptions about the role of air pollutants and infection in determining health outcomes (Figure 12). With each of the air pollutants, influenza infection has been shown to independently aggravate the prevalence of disease. Inadequate adjustment for influenza epidemics may thus confound interpretation of the impact of air pollutants on those health outcomes, particularly ARD admissions. However, the large impact of influenza on ARD risk estimates most likely results, in part, from influenza respiratory disease being included as a major component of ARD in the ICD category.

The traditional method adopted in air pollution and health studies to control for respiratory epidemics has been to use surrogate measures such as a dummy variable for influenza epidemics, based on the cutoff point of the 90th percentile of respiratory mortality distribution. This could lead to biased estimates because of the correlation between the epidemic measures and health outcomes and because of delays in the identification of epidemics (Braga et al. 2000; Touloumi et al. 2005). There is some question as to whether it is appropriate to include mortality on both

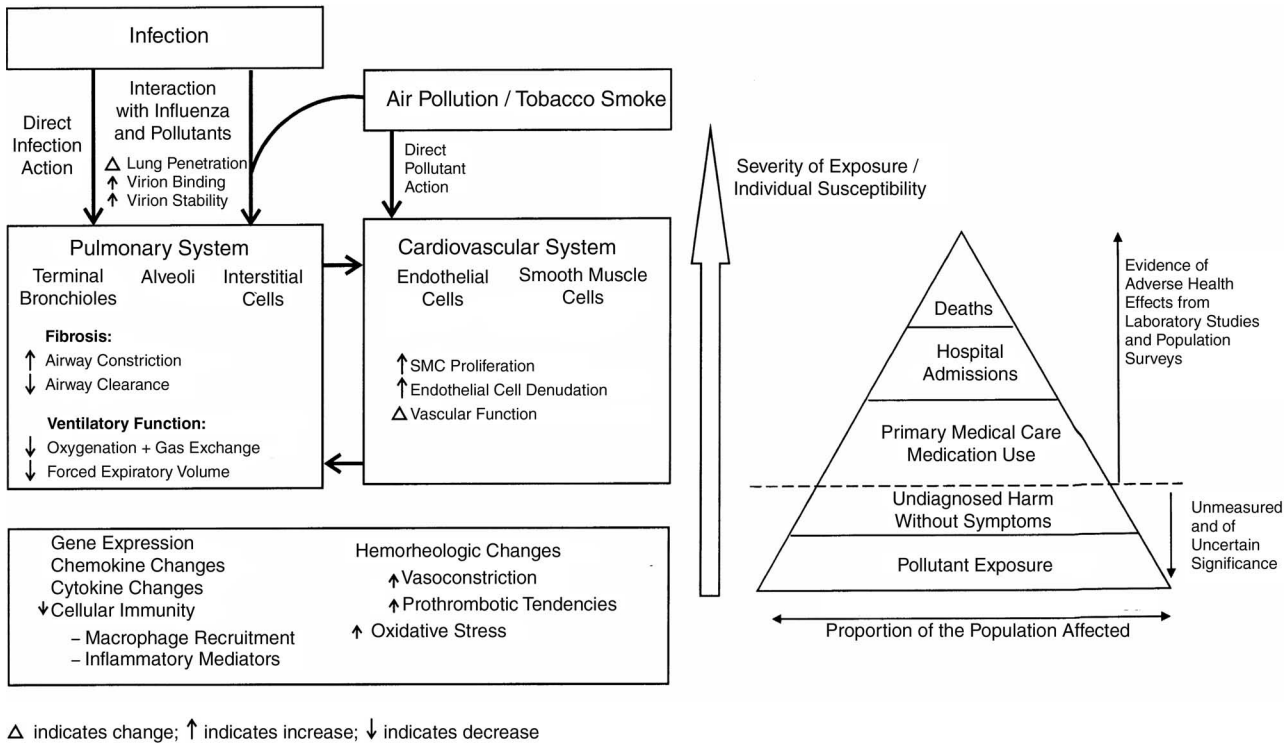

Figure 12. Flow chart showing hypothesis for causal paths between exposures to air pollution and influenza viruses, and their effects on health outcomes.

sides of the regression equations. Furthermore, defining a dummy variable as an indicator for influenza epidemics implies that all influenza activity has the same level of effect on health. It has been demonstrated, however, that there is heterogeneity in the effects of influenza epidemics on health (Braga et al. 2000). This heterogeneity could be explained by differences in the virulence and pathogenicity of the virions that were responsible for the outcomes in each specific period of epidemic. The use of virology data can help overcome some of the limitations of approaches based on mortality count to adjust for influenza epidemics and can also take into account other circulating respiratory viruses, such as RSV.

Although there is no widely accepted criterion for defining an influenza epidemic, in our study we defined an epidemic period as being recognized when the frequency of positive isolates exceeds the prior average frequency of positive isolates (known as the *epidemic threshold*). The beginning of an epidemic period can be identified only after two consecutive weeks with positive isolates above the threshold. A measure of influenza activity based on the proportion of laboratory-diagnosed positive isolates of influenza viruses has been shown to be applicable to air pollution studies (Wong CM et al. 2004; Chow et al. 2006).

A potential limitation of using the criterion based on a change in the estimate to define confounding is that it did not take into account the standard error of the estimate. The 0.1% cutoff point for confounding was based on 10% of the expected ER (in this case, 10%) per 10-μg/m^3 increase in pollutant concentrations, but there is no consensus on the cutoff value for determining confounding (Maldonado and Greenland 1993). It is expected that changing the cutoff value will ultimately affect the results. In a simulation study, Maldonado and Greenland (1993) compared the performance of several such criteria in fitting Poisson regression models to cohort data. They concluded that in terms of bias and root mean square error, the criterion based on change in the estimate of at least 0.1% performed best for determining confounders when the cutoff point value for deciding whether unadjusted and adjusted estimates differed was set at 10%. As with any simulation study, the results and conclusions of this study may apply only to situations that are similar to the simulated settings. Nevertheless, given the similarity of Poisson regression models employed in both simulation and time-series studies, we expect that the performance of the criterion based on change in the estimate in the simulation study would also apply to time-series studies.

We have shown that the associations between air pollutants and mortality and hospital admissions due to all natural and cardiovascular causes are unlikely to be confounded by influenza activity because of the modest change in the air pollution effects and the weak correlations between pollutant concentration levels and influenza activity. However, adjustment for influenza activity may reduce potential confounding for some effects of air pollutants on both mortality and hospital admissions due to respiratory causes and may help determine more valid effect estimates of air pollutants.

MODIFYING EFFECTS OF INFLUENZA

In this study, we found that SO_2 interacted with influenza to increase the ER of hospitalization for COPD and ARD, but not for RD and CVD. Inhalation of SO_2 at a concentration of 10 ppm (26.6 mg/m^3) after influenza virus infection increased the incidence of pneumonia in mice (Fairchild et al. 1972). Mice exposed to 10 ppm of SO_2 continuously for 72 hours showed loss of nasal cilia and decreased nasal mucosal thickness (Giddens and Fairchild 1972). These histopathologic changes were more severe in mice with mild upper-respiratory tract infections (Giddens and Fairchild 1972). In humans, an increased incidence of acute respiratory virus infection has been linked to elevated concentrations of SO_2 in epidemiologic studies (French et al. 1973). The damage caused by SO_2 to the human pulmonary defense system mainly lies in nonspecific airway reactivity, such as lower mucociliary transportation rate, decreased alveolar clearance of deposited particles, and compromised pulmonary macrophage function (Schlesinger 1999). People with hypersensitive airways, including COPD patients (Cazzola et al. 1991), are likely to be far more sensitive to SO_2 than healthy individuals (Schlesinger 1999), which may explain the positive interaction between SO_2 and influenza on hospitalization due to COPD.

The positive interactions between influenza and NO_2 in this study were found to be statistically significant for hospitalization from RD in the group of females aged 65+; ARD in the all-ages group of both males and females; and COPD in the female all-ages and 65+ groups (data not shown). A number of other studies have suggested a positive interaction between influenza and NO_2. For example, in one study, alveolar macrophages obtained from 4 of 9 human volunteers who had been continuously exposed to NO_2 at 0.60 ppm (1.15 mg/m^3) were found to be less effective in deactivating influenza viruses (Frampton et al. 1989). Similarly, concurrent exposure to a NO_2 concentration of 2 ppm during a rhinovirus infection has been shown to dramatically enhance the release of immunoregulatory cytokines in human nasal and bronchial epithelial cells (Spannhake et al. 2002). In addition, prior exposure to a NO_2 concentration of 2 ppm was demonstrated to greatly enhance exacerbation of asthma triggered by infection from respiratory viruses, including influenza (Chauhan et al. 2003).

In contrast, our results also detected the statistically significant negative interaction between influenza and NO_2 on hospitalization for RD in males in the all-ages group (data not shown). As supporting evidence for this negative interaction, another study using macrophages concluded there was no difference in the release of cytokines between the cells exposed to NO_2 at a concentration of 2 ppm and those to air (Devlin et al. 1999). Other studies did not detect any interaction between influenza and NO_2; for example, inhalation of NO_2 at 1 to 2 ppm for 2 hours per day for 3 consecutive days did not significantly increase vulnerability to influenza infections in young adults (Goings et al. 1989; Frampton et al. 2002). On the other hand, the effects of outdoor NO_2 could be biased by even higher levels of indoor NO_2 generated by the combustion process used in gas cooking, which may further render conflicting results in the interaction between NO_2 and influenza.

Our results identified a statistically significant negative interaction between PM_{10} and influenza in their effects on hospitalization for RD in the male, all-ages group in our separate analyses by sex (data not shown). Unlike other ambient air pollutants, PM_{10} has a rather complex and variable composition, mainly formed of sulfates, nitrates, a variety of metals, elemental carbon, and organic compounds (Brook et al. 2004). The complex nature of PM_{10} adds further difficulty to interpreting its health effects, and in fact, most studies have assessed only diesel emissions, a major source of PM_{10}, rather than overall ambient PM_{10} directly.

Our results suggest that O_3 statistically significantly interacts with influenza to increase the ER of hospitalization for RD, ARD, and COPD in either the all-age group or 65+ group, or both. O_3 is a strong oxidative agent and a potent pulmonary irritant. There is ample laboratory evidence to support the positive interaction between O_3 and influenza. For example, exposure to O_3 at 0.2 ppm (0.4 $\mu g/m^3$) has been reported to increase the efficiency of rhinovirus infection from 41% to 67% in respiratory epithelial cells, and this effect can be attenuated by the use of antioxidants (Spannhake et al. 2002). Exposure to O_3 at 0.2 ppm markedly increased adhesion of polymorphonuclear leukocytes to human tracheal epithelial cells (Tosi et al. 1994). Similarly, in mice, continuous exposure to O_3 at 0.5 ppm attenuated acute lung damage during early influenza infection, but exacerbated long-term lung injury (Jakab and Bassett 1990). Another study in young male adult humans showed that intermittent exposure to O_3 at 0.3 ppm after infection by rhinovirus did not markedly change adhesion of polymorphonuclear leukocytes to the nasal epithelium or levels of interferon (Henderson et al. 1988).

Since both air pollutants and the influenza virus need to interact with respiratory epithelial cells to cause harm, the relationship between the two could be either competitive or influenced by a saturation effect. Therefore, if one factor saturates a particular pathway, there may be no possibility for the other to demonstrate any additive effect. As evidence for this theory, early studies in mice showed that exposure to O_3 (0.9 ppm for 3 hours) and SO_2 (6 ppm for 7 days) could almost completely or partially inhibit influenza virus growth in the nasal cavity (Andersen et al. 1977; Fairchild 1977). Similarly, a high dose of NO_2 (1.5 ppm) could suppress the replication and release of RSV in human bronchial epithelial cells (Becker and Soukup 1999). A slight reduction of pneumonia cases was also observed after influenza-infected mice were exposed to SO_2 at low concentrations (less than 10 ppm) (Fairchild et al. 1972). Existing laboratory studies of the potential synergistic or even competitive relationship between air pollutants and influenza virus have not yet provided a plausible mechanism for any interaction between them. However, the concentrations of pollutants in animal and human laboratory studies are 10 to 1000 times higher than the average ambient levels observed in Hong Kong during the period of this study. Therefore, epidemiologic studies have the potential to provide plausible hypotheses more at the population level, which can be further tested in animal models.

In this analysis, we did not detect any statistically significant interaction between influenza and any of the air pollutants studied in terms of their effects on mortality and hospitalization due to CVD. This may be because our study assesses only the short-term effects of influenza and air pollutants. It is, however, not worthwhile to try to separate the effects of individual air pollutants, as they frequently react with each other. For example, NO_2 can be photolyzed into NO and oxygen atoms, the latter of which combine with molecular oxygen to form O_3 (Brook et al. 2004). Future laboratory studies may provide further insight into the mechanisms of any possible interaction between influenza and air pollution.

EFFECTS OF AIR POLLUTION IN SOCIALLY DEPRIVED URBAN AREAS

In six regions of São Paulo, Brazil, the effects of PM_{10} on daily respiratory deaths were negatively correlated with the percentage of people with college education and the percentage of people with high family income, and were positively associated with the percentage of people living in slums (Martins et al. 2004). This suggests that social deprivation represents an effect modifier of the association between air pollution and respiratory deaths. In the city of Hamilton, Canada, which was divided into five zones based on proximity to fixed-site air pollution monitors, SO_2 and the coefficient of haze (regarded as a measure for

particulate pollution) were associated with increased mortality. Mortality was higher in those zones with lower socioeconomic characteristics, lower educational attainment, and a higher level of employment in manufacturing (Jerrett et al. 2004). In the Hamilton Metropolitan Census Area, subjects in the more deprived neighborhoods had greater exposure to ambient PM, gaseous pollutants, and traffic. At least some of the observed social gradients in circulatory mortality arise from inequalities in environmental health in terms of exposure to background and traffic-related air pollutants (Finkelstein et al. 2005). In our study, residence in areas of higher social deprivation was also associated with cardiovascular mortality, potentially due to exposure to gaseous air pollution.

Furthermore, a meta-analysis of the short-term health effects of air pollution (specifically, SO_2, NO_2, CO, PM_{10}, and O_3) in eight Italian cities showed that the ERs for hospital admission were modified by a social deprivation score and by the NO_2/PM_{10} ratio (Biggeri et al. 2004). In another study, carbon monoxide was found to have a statistically significant effect on increases in hospitalizations of children aged 1 to 18, and the effect of pollution was found to be greater for children with lower socioeconomic status (Neidell 2004). However, in Hong Kong, the inverse health care phenomenon (that those with greater health need receive less health care) may apply, as social deprivation was found to be negatively related to hospitalization and positively related to mortality (Wong CM et al. 1999a). In the present study, an association between social deprivation and hospitalization related to air pollution was not observed. Besides lower accessibility to hospital services for people of lower socioeconomic level, there may be additional explanations for the lack of interaction between social deprivation and hospitalization, including measurement errors and errors in the coding of addresses of patients and in the TPU codes. Further work is required, including implementing geographic information system techniques in the mapping of addresses to coordinates and to TPUs, which is beyond the scope of this study.

Hong Kong is an affluent city in the Asia-Pacific region, but poverty is still an important problem in some subgroups of the population, creating social disparities and weakening community coherence. In such socially deprived areas, violence and suicide rates are typically higher, and people are in poorer health (Kawachi and Berkman 2000). An SDI is needed to identify socially deprived areas so that additional community and health resources can be allocated and environmental protection needs assessed.

In this study, we used six demographic variables, available from the census; each variable belongs to a different aspect of socioeconomic status. Similar variables have been used in other well-known SDIs in other countries. For example, in a comparison of our index with other social deprivation indices such as the U.K. Department of Environment Index of Local Conditions (UK DOE 1994), Townsend (Payne et al. 1996; Benach et al. 2001), Jarman (Jarman 1983), and LWT Breadline Britain indices (Payne et al. 1996), "unemployment proportion" is similar to "unemployment rate"; "subtenant" is similar to "not owner occupied households"; "never-married" is similar to "lone parent household"; "one person household" is similar to "lone pensioner"; and "no school" is similar to "low GCSE attainment." These variables are related to material deprivation (Benach et al. 2001) (e.g., unemployment, monthly household income < U.S. $250, and no schooling), lack of family and social connection (e.g., never-married and one-person household), or lack of adequate facility in living quarters (e.g., subtenant). Socioeconomic factors are usually multidimensional, and some of them, such as low income and low education, may be correlated with each other. Instead of studying several factors individually, we used an index derived from an average of six measures of social deprivation, which would be likely to quantify disadvantages in terms of one or more of these three aspects of social deprivation. We assigned a neighborhood-level SDI score to each subject based on the TPU code of his or her residency at the time of death.

The effects of both ambient air pollution and socioeconomic position on health are well documented. The socioeconomic status of an individual and his or her area of residence may play a role in the epidemiology of disease and death associated with exposure to air pollution (O'Neill et al. 2003). Together with the evidence that poor and working-class communities are often more exposed to air pollution, the results of these studies should provide evidence to promote discussion among scientists, policy makers, and the public about these disparities in health (Hedley et al. 2008).

There are several limitations associated with our study. First, we are aware that the SDI we defined in this study may not reflect the whole profile of deprivation, although all of the information available from the Census is included in the computation. Second, there may be heterogeneity within local areas with the same SDI level, which has not been accounted for. However, since the categories of deprivation we defined are broad, the results of this study should be robust. Third, population-level exposures using average concentrations from air pollution monitors as a proxy for each individual exposure may be subject to some measurement errors. Consequently, we cannot test the hypothesis that the increased pollution-related mortality risk in high SDI areas is partly due to more exposure to air pollution. However, because the Hong Kong population is

very dense (about 6200 people/km^2 on average, ranging to more than 100,000 people/km^2), the air pollution levels between geographic areas are highly correlated, and because we used averaged air pollutant concentrations from as many as eight monitoring stations, we believe that the aggregated daily concentrations derived for the whole of Hong Kong should be at least as reliable as those in other daily time-series air pollution studies. Finally, the underlying mechanisms that determine why some population groups with a high SDI score experience greater adverse effects from air pollution are still unclear. In order to be able to make decisions about specific interventions for protecting health, mechanism studies should be given high priority.

SHORT-TERM EFFECTS OF AIR POLLUTION

In our study, the main effect estimates of air pollutants for both mortality and hospitalization appeared robust to different degrees of control of seasonality and time trend using different degrees of freedom in spline smoothing functions of time, except those for SO_2. However, there were substantial reductions in the ER estimates when additional adjustment for temperature at longer lags was added to the core model, with temperature predefined to be at the current day. The magnitude of the reduction (with a change in the ER [%] ranging from 0.1 to 0.6) varied from pollutant to pollutant (data not shown). However, in Hong Kong, residual confounding due to a lack of additional adjustment for temperature at longer lags is unlikely, since the correlation between the residual from the model adjusted for temperature at lag 0 and the temperature itself at each 1–7 lag day is low (less than 0.1 in all models). In addition, the correlation between the temperature at lag 0 day and the temperature at longer lags is high (around 0.9). There would be a problem of multi-collinearity (Ramsay et al. 2003) if we included temperature at longer lags in the core model. Therefore, we did not adjust for temperature at longer lags in the core model and predefined temperature to be that of lag 0 day, according to the protocol jointly agreed to by all the PAPA teams (see the Common Protocol at the end of this volume).

In Hong Kong, studies with different designs conducted since 1991 have demonstrated the adverse effects of air pollution on mortality, hospital admissions, primary care consultations, and the respiratory health of young children. In cross-sectional studies, Ong and colleagues (1991), Tam and colleagues (1994), and Yu and colleagues (2001) found that primary school children with high exposures to air pollution in mixed industrial and residential areas had statistically significantly higher risks of respiratory morbidity, including sore throat, cough, wheezing, and bronchial hyperreactivity. These findings were further confirmed by cohort studies that showed a reduction in bronchitis symptoms (Peters et al. 1996; Wong CM et al. 1998, 1999b) and cardio-respiratory mortality (Hedley et al. 2002) before and after the government-mandated restriction of sulfur content in fuel. Several time-series studies in Hong Kong on the health impact of air pollution, including on mortality (Wong CM et al. 2001; Wong TW et al. 2002) and hospital admissions (Wong CM et al. 1999c, 2002; Wong GWK et al. 2001; Wong TW et al. 1999), have consistently shown that CVD and RD are associated with air pollution in this region. These results were obtained using internationally recognized methods in the same population during different study periods.

The current PAPA study results are consistent with our previous two milestone studies (Wong CM et al. 2001, 2002) and confirm that higher concentrations of air pollution are directly associated with higher population risks of mortality and hospitalizations due to cardio-respiratory diseases.

Mortality due to accidental causes has been widely used as a control for the study of effects of air pollution. The nonsignificant results for this health outcome in this study thus support the validity of the study's results. However, the analysis of the effects of air pollutants on the other potential control diseases in this study (i.e., non-cardiopulmonary diseases excluding accidental causes of deaths) showed some degree of positive association with air pollution, indicating that persons who die from non-cardiopulmonary diseases may also be vulnerable to the effects of air pollution and that the effects of air pollution are most likely nonspecific regarding cause of death. Air pollution may affect susceptible persons with comorbidity not specific to cardiopulmonary diseases. However, the biologic mechanisms are not clear and deserve further investigation.

NO_2

Our findings raise questions about the role of individual pollutants in relation to health outcomes. The pattern and strength of associations between NO_2 and mortality due to all natural causes, CVD (including cardiac diseases and stroke), and RD (including LRI and COPD) support the hypothesis that NO_2, in the concentrations observed in Hong Kong, is detrimental to health. The few studies of the association between NO_2 and mortality due to CVD and RD in Asia include several time-series studies from China (Chang et al. 2003) and South Korea (Kwon et al. 2001; Hong et al. 2002a, 2002b), as well as previous Hong Kong studies (Wong CM et al. 2001; Wong TW 2002). In another Hong Kong study, G. W. K. Wong and colleagues (Wong GWK 2001) obtained results consistent with this study.

NO_2 was also strongly associated with hospital admissions in both the CVD (except stroke) and RD groups, for all ages; ARD in the 0–14 age group; and ALRI in the 0–14 age group. Our findings are again consistent with numerous time-series studies in China (Hwang and Chan 2002; Chang et al. 2003), India (Pande et al. 2002), Japan (Tanaka et al. 1998; Ye et al. 2001), and South Korea (Cho et al. 2000; Lee et al. 2002), and with the previous Hong Kong findings (Wong TW et al. 1999; Wong CM et al. 2002). In addition, our results indicate the vulnerability of those at the extremes of the age range in that the elderly (aged 65+) were particularly susceptible to the NO_2 effect on COPD admissions, while children (aged 0–14) were susceptible to the NO_2 effect on asthma admissions. The larger effects found in the susceptible age groups were consistent with the findings in the previous Hong Kong study by C. M. Wong and colleagues (1999b).

SO_2

Sulfur dioxide showed an association with all the cardiopulmonary outcomes under study except stroke and COPD. Numerous time-series studies published over the past few decades support the adverse health effects of SO_2, including studies from China (Gao 1993; Xu X et al. 1994; Xu Z et al. 2000; Chang et al. 2003; Venners et al. 2003) and South Korea (Hong et al. 1999, 2002a, 2002b; Lee et al. 1999, 2000; Kwon et al. 2001). They also include case-crossover (Kan and Chen 2003) and ecologic (Xu ZY et al. 1996) studies, both conducted in China; the previous Hong Kong study (Wong CM et al. 2001); and another Hong Kong study by C. M. Wong and associates (1999b) showing, in particular, greater risk in the older population. Furthermore, our results from the current study were also consistent with other previous Hong Kong studies concerning reductions in both respiratory morbidity and cardio-respiratory mortality after the decline in SO_2 following sulfur content restriction in fuel (Peters et al. 1996; Wong CM et al. 1998; Hedley et al. 2002, 2004).

The biologic mechanism of the effect of SO_2 on human health may explain our findings for the older population (65+). COPD is characterized by hyperreactive airways and exacerbations that typically present with a rapid progression of chronic symptoms (Pauwels et al. 2001). Classically, an exacerbation is noted by increased shortness of breath, wheezing, and sputum production. On the other hand, normal healthy individuals show minimal, if any, significant alterations in pulmonary functional indices and some upper respiratory symptoms after exposure to SO_2 at $\leq$ 13.1 mg/m^3 for durations of less than 1 to 4 hours (US EPA 1982, 1986; Sheppard 1988). However, when people with hyperactive airways are exposed to SO_2 at 0.66 to 1.3 mg/m^3, they show a striking acute response, characterized by bronchoconstriction, increased airway resistance, and decreased expiratory flow rates, as well as the clinical symptoms of wheezing and shortness of breath (Sheppard 1988). The experimental concentrations in the EPA and Sheppard studies are a hundred- to a thousandfold greater than the ambient concentration level we breathe. Therefore, people admitted to hospitals because of COPD might be those with hyperactive airways who were susceptible to SO_2 effects. This effect of SO_2 may partly explain the strong statistical significance in our results for COPD, but there is no apparent evidence to support the lack of statistical significance in our results for ARD, ALRI, and asthma. Nevertheless, our findings of the association between SO_2 and COPD admissions are consistent with the previous time-series study in Hong Kong (Wong TW et al. 1999) and are supported by an Indian time-series study by Pande and coworkers (2002).

In addition, we suspect the nonsignificant results in some of the respiratory categories may be due to errors in exposure measurement and spatial variations. However, deletion of some monitoring stations that exhibited observable heterogeneity, such as station 6 and 8, produced only small changes in ER (within 0.1%). In future studies, a two-stage regression model (Krewski et al. 2003) capable of accounting for spatial heterogeneity might be applied.

PM_{10}

PM_{10} showed a statistically significant association with all-cause, cardiovascular-related, and respiratory-related mortality in our study. These associations have been found in other Asian cities, such as Beijing (Chang et al. 2003), Inchon and Seoul (Hong et al. 1999; Kwon et al. 2001), and Bangkok (Ostro et al. 1999), but no significant associations for respiratory mortality were detected in Kaohsiung, Taiwan (Tsai et al. 2003), using case-crossover analysis. Overall, the combined PM_{10} estimates for three systematic reviews of the United States (Samet et al. 2000b; HEI 2003), Europe (WHO 2004a), and Asia (HEI International Scientific Oversight Committee 2004) showed ER (%) estimates (range, 0.5 to 1.2) overlapping those in Hong Kong (0.37 to 1.02).

PM_{10} effects on hospitalizations have been clearly demonstrated in this PAPA analysis, and the results are consistent with another Hong Kong study (Wong TW et al. 1999) and a study in Taiwan (Hwang and Chan 2002). Both Asian studies and a U.S. study (Samet et al. 2000a) have indicated that people aged 65+ were the most susceptible group. In our study, we also showed that the elderly are at greater risk of hospital admissions due to CVD and RD, as indicated by the higher ER (except for COPD) for this age group than that for the overall population.

O_3

The association between O_3 and mortality due to all causes was statistically significant in our study. A recent study of Shanghai (Zhang et al. 2006) reported that O_3 was associated with total and cardiovascular-related mortality, especially in the cold season. These findings are consistent with both our present and previous studies (Wong CM et al. 2002). There is no statistically significant association between O_3 and LRI, and limited information could be found on the biologic mechanism for the health effects of O_3 that might interpret the epidemiologic findings in this study. The findings of previous studies in both Asian (Hong et al. 1999; Kwon et al. 2001) and Western cities (Anderson et al. 2001; Goldberg et al. 2001) were inconsistent.

O_3 was highly associated with respiratory-related mortality and all subcategories of RD (ARD, ALRI, COPD, and asthma) in all the age groups in this study. For cardiovascular-related hospitalizations, no statistically significant association was found. There are a limited number of studies of the effects of O_3 on hospitalizations in Asian cities. Apart from the studies in Hong Kong, most Asian studies (Tanaka et al. 1998; Kuo et al. 2002; Lee et al. 2002) showed an association between O_3 and hospitalizations due to asthma.

IMPLICATIONS OF FINDINGS AND CONCLUSIONS

This study is the first to assess three different measures of influenza activity using the same statistical model and to show that effect estimates of influenza-associated mortality and hospital admissions were consistent. Given that the gold standard for the diagnosis of respiratory virus infections is based on virology data, the use of virology data to measure influenza activity in three different ways and the consistent results among these measures further strengthen the validity of the assessment of the disease burden of influenza in our study.

Most health outcomes did not appear to be confounded by the influenza viruses to an extent $\geq 10\%$ of the expected effect size. Although the magnitude of the effect of the pollutants changed, the association with health outcomes was not modified and remained robust to adjustment of influenza activity, which lends support to the argument for causality in the association of air pollution and health outcomes. Our data suggest that sensitivity analyses, with and without adjustment for influenza epidemics, may demonstrate potential confounding and help determine a more reliable range for estimates of the effects of air pollutants.

In this first epidemiologic study on the interaction between air pollution and influenza activity, we showed that influenza modified the effects of air pollution on respiratory and cardiovascular morbidity. The results provide evidence to support a hypothesis, demonstrated in animal studies, for a possible link between air pollution and influenza activity in terms of health effects. Further research is needed to clarify under what conditions there would be observable interactions between the effects of air pollution and influenza and to strengthen the argument for causality.

This study also showed that residence in socially deprived areas is related to additional risks of air pollution. An SDI, as used in this study, can identify relatively deprived areas so that additional environmental protection measures and health resources can be allocated. Policy makers should take into account social disparities when setting policy for urban development.

Finally, we can have confidence that, in most cases, an assessment of the ER of air pollution, without adjustment for influenza activity, will uncover variations in the estimates only to within 0.1%. We should also be aware that effect modification due to circulation of influenza viruses may be present. Estimation of risks without taking effect modification into account would produce population average estimates that did not reflect risks, which may vary substantially from situation to situation.

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APPENDIX A. Technical Summary of Methods

STATISTICAL SOFTWARE

We used the statistical software package R, version 2.5.1 (R Development Core team 2007) with mgcv, version 1.3-25.

MODELING

Core Model

Variations in the daily counts of health outcomes (mortality and hospital admissions) were modeled with a quasi-likelihood Poisson regression. Covariates of the core model included time trend, indicators for each day of the week, temperature, RH, and special periods (e.g., public holidays). Overdispersion was also taken into account.

To filter out seasonal patterns and the long-term trend of daily health outcomes, we used natural spline smoothing on time trend, temperature, and RH. For a smoothing function for time trend, we fixed the degrees of freedom at 4 to 6 per year. For a smoothing function for temperature and RH, we fixed the degrees of freedom at 3. We then checked the randomness of residual plots and that the PACF plots of the first two peaks were within the 95% CI. The core model was considered adequate when it met these criteria. The following is the R command:

R command:

```
core.model<-gam(outcome ~ s(trend,
k=dfperyear+1, fx=T, bs="cr") + s(temp, k=df2+1,
fx=T, bs="cr") + s(hum, k=df3+1, fx=T, bs="cr")
+ I1 + I2 + I3 + I4 + I5 + I6 + holiday,
control=gam.control(maxit=100,globit=20,trace=F),
family=quasipoisson, na.action=na.omit)
```

The definitions of the variables were as follows: outcome = daily counts of mortality and hospital admissions; trend = long-term time trends; temp = daily temperature; hum = daily RH; I1–I6 = dummy variables indicating the day of the week corresponding to Monday through Saturday; holiday = public holiday.

PACF Plots

The Pearson residuals were used to plot the PACF, using the following code:

R command:

```
model.resid<-resid(core.model,
type="scaled.pearson")
check.model.pacf<-acf(model.resid,
lag.max = 30, type = c("partial"), plot=F,
na.action = na.pass)
ci<-qnorm(.975)/sqrt(check.model.pacf$n.used)
plot(1:30, as.numeric(check.model.pacf[[1]]),
xlab="", ylab="",
ylim=range(as.numeric(check.model.pacf[[1]]),
ci, -ci, 0.1, -0.1), type="n", axes=F)
segments(1:30, rep(0,30), 1:30,
as.numeric(check.model.pacf[[1]]))
axis(1,cex.axis=1.0)
axis(2,cex.axis=1.0)
abline(h=c(0, ci, -ci, 0.1, -0.1),
lty=c(1,2,2,3,3), col=c(1,4,4,2,2))
box()
```

The definitions of the variables were as follows: model.resid = Pearson residuals adjusted with scaled parameter; check.model.pacf = PACF values corresponding to lag 1 to 30 days; ci = the 95% confidence interval upper bound of the PACF.

Model for Main Effects of Pollutants

After development of the core model, the daily pollutant variable was entered into the model. The main effects of the pollutants were estimated using the coefficient of the variable "pollutant":

R command:

```
air_model1<-update(core.model, . ~ .
+ pollutant, sp=core.model$sp,
na.action=na.omit)
```

The definitions of the variables were as follows: pollutant = daily pollutant variable (with possible different lag days defined).

Model for Main Effects of Influenza

There were three measures of influenza activity. After development of the core model, the daily RSV and one measure of influenza activity were entered into the model. We repeated the same procedure for each measure of influenza activity. The main effects of influenza were estimated using the coefficient of variable "influ":

R command:

```
infl_model<-update(core.model, . ~ . + rsv
+ influ, sp=core.model$sp, na.action=na.omit)
```

The definitions of the variables were as follows: rsv = daily RSV variable; influ = daily influenza variable (with three different influenza measures defined).

Model for Confounding Effects of Influenza on Pollutants

After development of the core model, the daily RSV, influenza, and pollutant variables were entered into the model at the same time. The confounding effects of influenza on pollutants were assessed by adjusting the estimates of pollutants for influenza. We compared the estimates with the main effects of pollutants to assess whether there were any changes in the effect estimates indicating that there was confounding.

R command:

```
air_model2<-update(core.model, . ~ .
+ rsv + influ + pollutant, sp=core.model$sp,
na.action=na.omit)
```

Model for Interaction Effects Between Pollutants and Influenza

After development of the finalized core model, the daily RSV, influenza, and pollutant variables — as well as the interaction terms between pollutants and influenza (defined by the product term of these two variables) — were entered into the model. The interaction effects were estimated using the coefficient of the interaction terms.

R command:

```
air_model3<- update(core.model, . ~ .
+ rsv + influ * pollutant, sp=core.model$sp,
na.action=na.omit)
```

ESTIMATE OF THE ER PER 10-μg/m^3 INCREASE AND CALCULATION OF THE 95% CI

All estimates were converted into the ER per 10-μg/m^3 increase, and their corresponding 95% CIs were calculated using the following code:

R command:

```
er<-round((exp(estimate*10)-1)*100,2)
lowb<-round((exp((estimate-qnorm(.975)*se.est)
*10)-1)*100,2)
uppb<-round((exp((estimate+qnorm(.975)*se.est)
*10)-1)*100,2)
print(c(er, lowb, uppb))
```

The definitions of the variables were as follows: estimate = the parameter estimates corresponding to different models; se.est = the standard error of parameter estimates.

OVERDISPERSION PARAMETER

The overdispersion parameter in the core model was extracted using the following R command:

R command:

```
Disp_para<-round(summary(core.model$disp,2))
```

TEST OF NONLINEARITY CONCENTRATION–RESPONSE CURVES

After development of the core model, a natural spline smoothing function with fixed degrees of freedom of 3 for pollutants was entered into the model (smooth_model). We compared the deviance between smooth_model and the air_model1, which follows a chi-square distribution with 2 dfs. If the *P* value of the test statistic was ≤ 0.05 for each concentration–response curve, we concluded that the concentration–response curve was nonlinear.

R command:

```
smooth_model<-update(core.model, . ~ .
+ s(pollutant, k=3+1, fx=T, bs="cr"),
sp=core.model$sp, na.action=na.omit)
reduce.mod<- air_model1$dev
full.mod<- smooth_model$dev
chi.stat<-round(reduce.mod-full.mod,2)
pvalue<-round(1-pchisq(chi.stat,df-2),4)
print(c(chi.stat, pvalue))
```

The definitions of the variables were as follows: smooth_model = the model with 3 df using a smoothing function for air pollutants; reduce_mod = the model deviance of linear effect assumption on air pollutants; full_mod = the model deviance of smoothed assumption on air pollutants.

APPENDIX B. Location of Air Monitoring Stations in Hong Kong

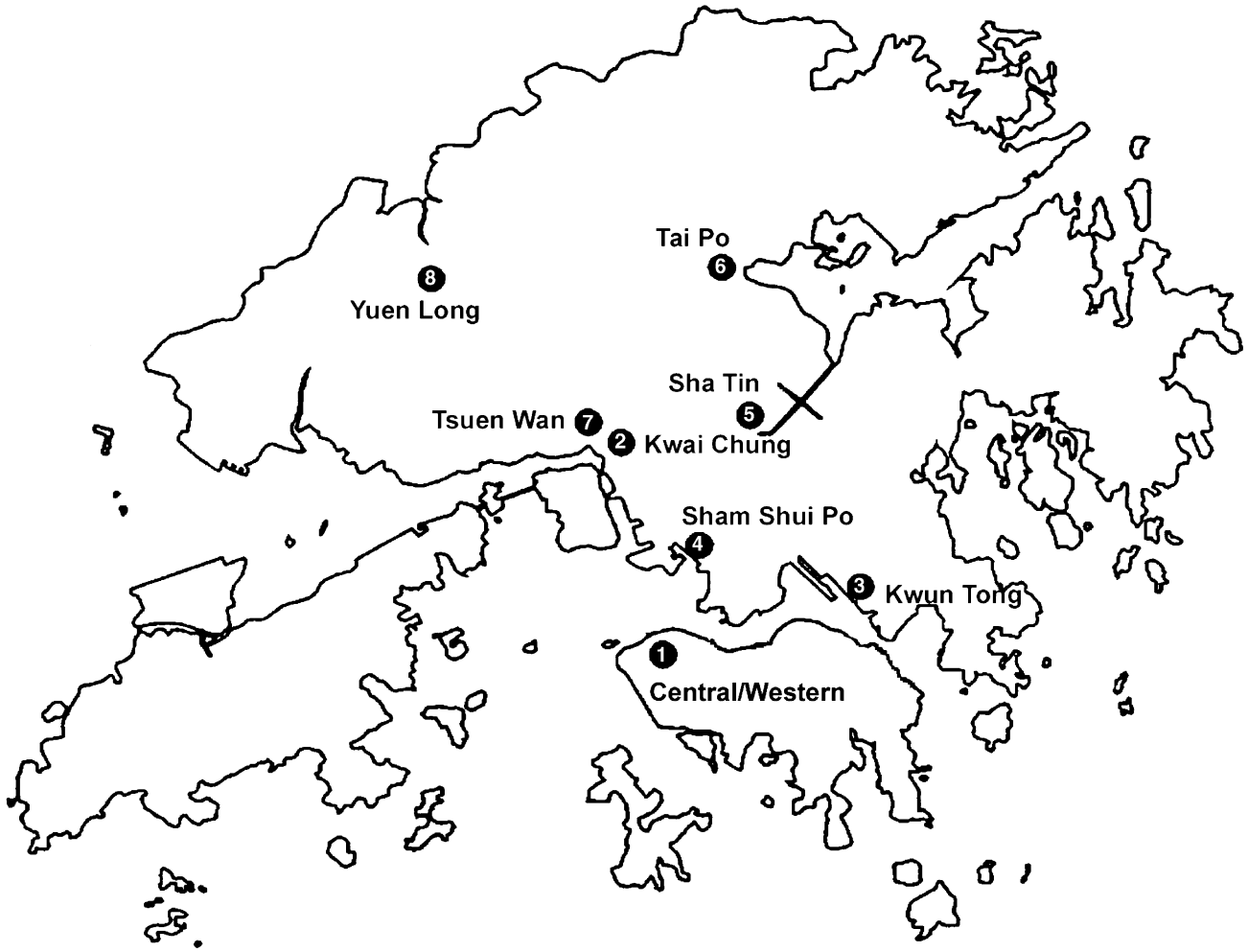

Figure B.1. Map of Hong Kong showing locations of air monitors. All eight stations measured the four criteria air pollutants (NO_2, SO_2, PM_{10}, and O_3). O_3 measurements from station 3 — which had hourly data that were less than 75% complete during the study period — were excluded from the analysis.

APPENDIX C. Equipment Used to Measure Characteristics of Pollutants

	Pollutant			
	NO_2	SO_2	PM_{10}	O_3
Equipment / Manufacturer	API (model 200A) / Opsis AB	TECO (model 43A) / Opsis AB	TEOM series 1400a–AB / Rupprecht & Patashnick	API (model 400 or 400A) / Opsis AB
Method of measurement	Chemiluminescence/ differential optical absorption spectroscopy	Fluorescence / differential optical absorption spectroscopy	Tapered element oscillating microbalance	UV absorption / differential optical absorption spectroscopy
Concentration unit	ppb	ppb	$\mu g/m^3$	ppb

APPENDIX D. Death Documentation and Mortality Statistics in Hong Kong

In Hong Kong, a death registration system is in place to register and collect information related to deaths occurring locally. All deaths are categorized into 2 types, namely, reportable deaths and non-reportable deaths, for which the cause of death will be certified by a coroner or an attending medical practitioner, respectively.

Reportable deaths: After a thorough investigation, the coroner formally informs the Immigration Department (ImmD) of the cause(s) of death for the death registration.

Non-reportable deaths: The deceased's relative brings the death certificate to the ImmD for registration of the death. After collecting the information, the ImmD sets up a mortality database and sends the information to the Department of Health (DH) and the Census & Statistics Department (C&SD). The DH verifies the coding for the underlying cause of death according to the International Classification of Diseases (ICD-10, or ICD-9 before year 2001). The amended database is then sent to the C&SD for compilation of the mortality statistics. The DH and C&SD prepare relevant publications for general dissemination. A simplified flow chart of the death documentation system is shown in the diagram in Figure D.1.

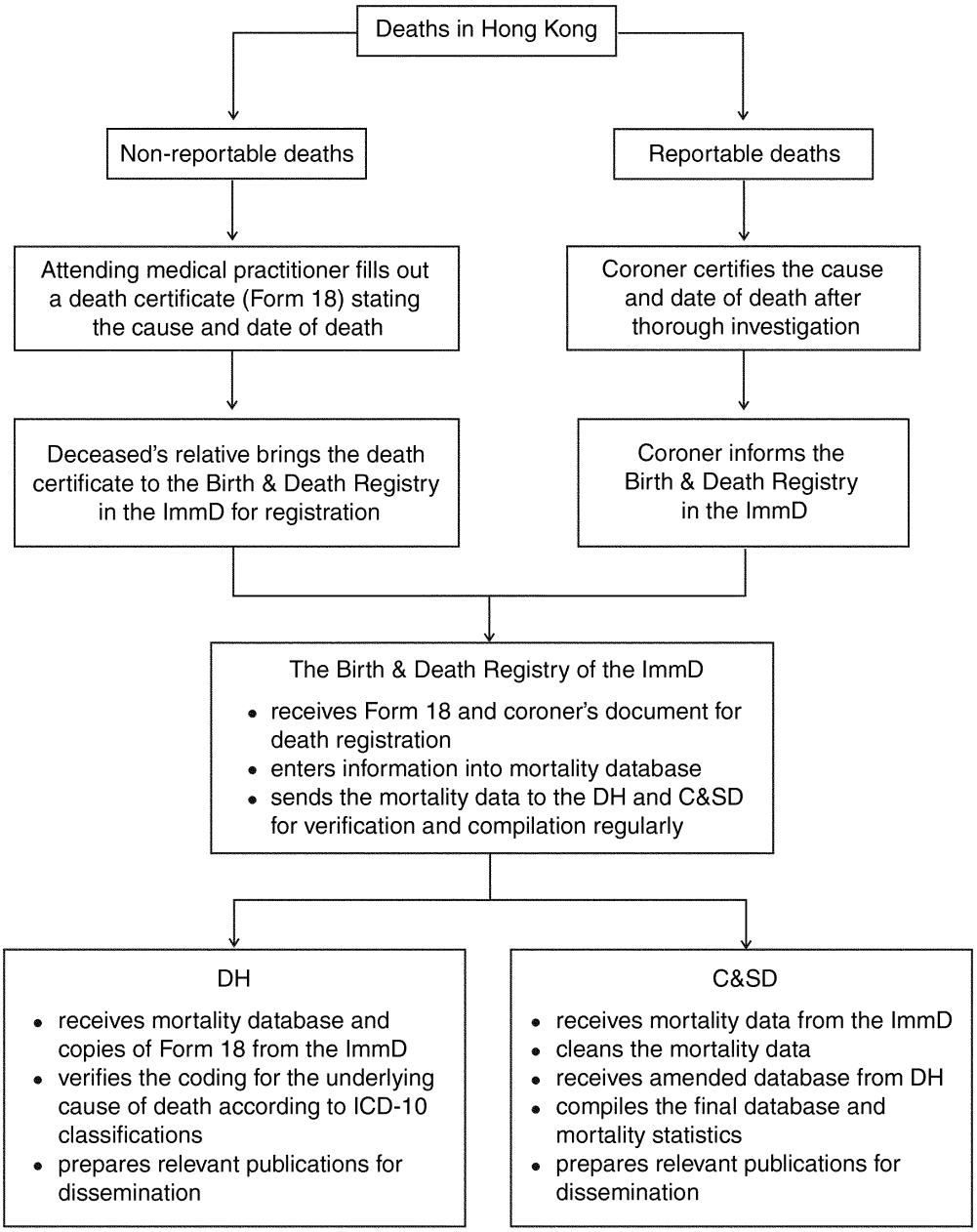

Figure D.1. Flow chart showing documentation of deaths and compilation of mortality statistics in Hong Kong.

APPENDIX E. Residuals Plots and Residuals PACF Plots of Mortality

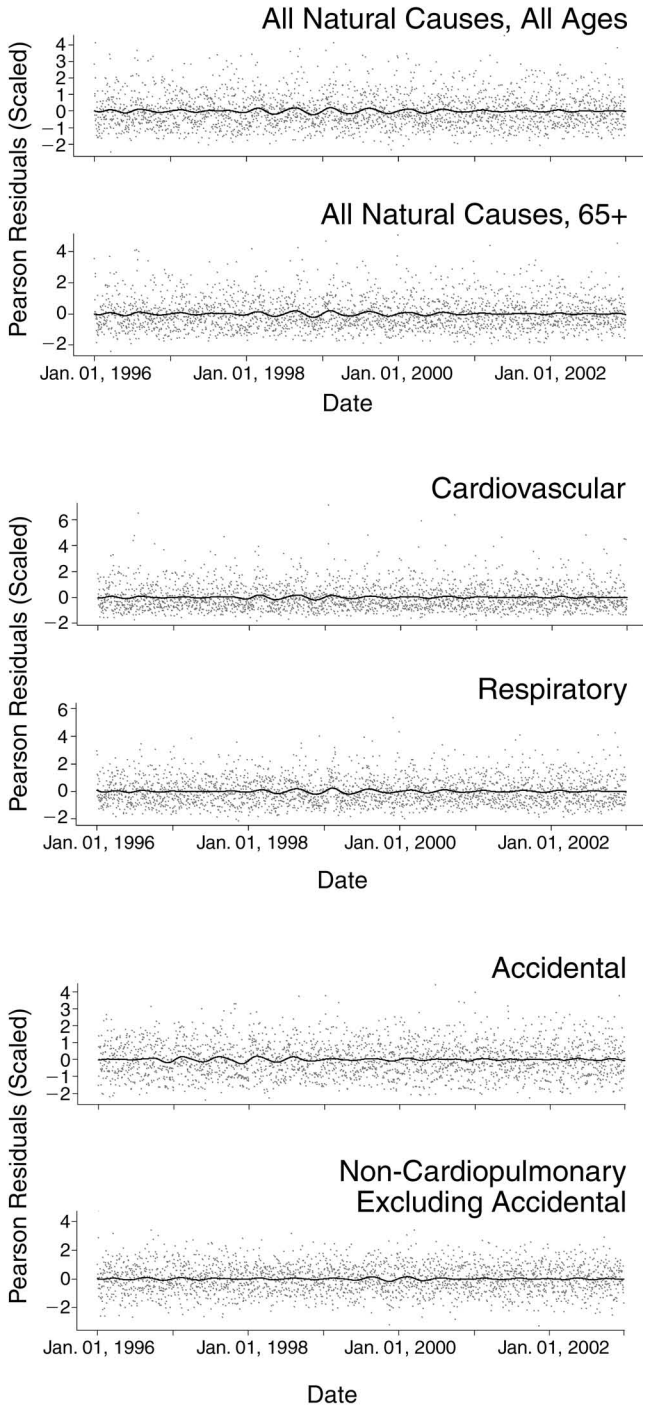

Figure E.1. Residuals plots of mortality, using cubic smoothing splines with 35 df, by cause of death.

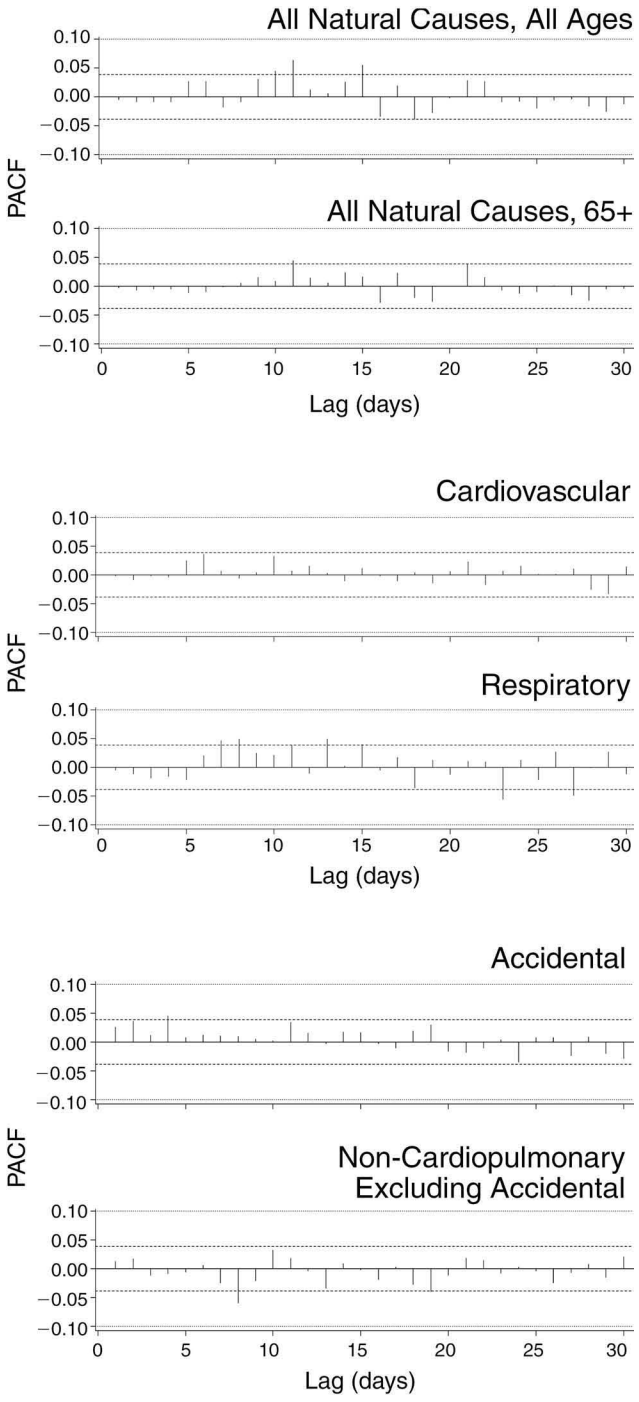

Figure E.2. Residuals PACF plots of mortality, by cause of death.

APPENDIX F. Residuals Plots and Residuals PACF Plots of Cardiovascular- and Respiratory-Related Hospitalizations

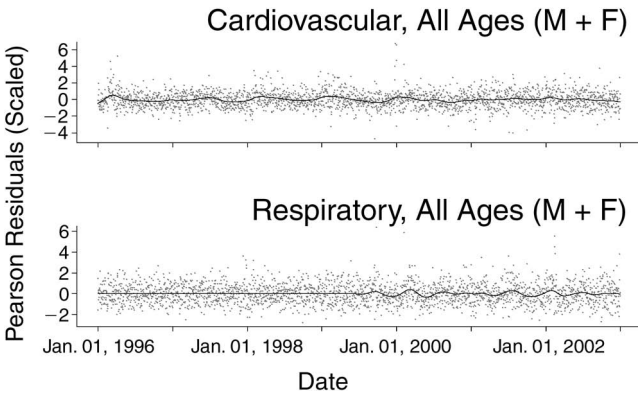

Figure F.1. Residuals plots of cardiovascular- and respiratory-related hospitalizations, using cubic smoothing splines with 42 df.

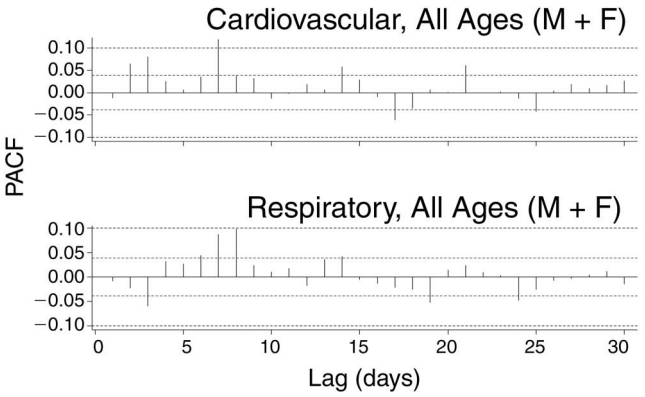

Figure F.2. Residuals PACF plots of cardiovascular- and respiratory-related hospitalizations.

APPENDIX G. Summary Statistics and Rates for Daily Mortality and Hospitalization Outcomes by Three Levels of Social Deprivation, 1996–2002[a]

	Minimum	1st Quarter	Median	Mean	3rd Quarter	Maximum	SD	Rates
Mortality (Deaths / Day)								
All natural causes								
Low SDI	5.0	16.0	19.0	19.3	23.0	46.0	5.3	330.7
Middle SDI	13.0	31.0	36.0	36.2	42.0	66.0	8.0	471.7
High SDI	3.0	13.0	17.0	17.4	21.0	40.0	5.4	596.5
Cardiovascular								
Low SDI	0.0	3.0	5.0	5.3	7.0	23.0	2.6	86.1
Middle SDI	1.0	7.0	10.0	10.1	12.0	28.0	3.9	126.2
High SDI	0.0	3.0	5.0	5.0	6.0	15.0	2.5	162.7
Respiratory								
Low SDI	0.0	2.0	3.0	3.3	4.0	11.0	1.9	53.4
Middle SDI	0.0	5.0	6.0	6.7	9.0	17.0	2.9	82.9
High SDI	0.0	2.0	3.0	3.5	5.0	13.0	2.0	114.3
Hospitalization (Admissions / Day)								
Cardiovascular								
Low SDI	6.0	24.0	30.0	30.1	36.0	58.0	8.8	527.1
Middle SDI	16.0	36.0	45.0	46.1	55.0	94.0	12.6	638.8
High SDI	7.0	21.0	27.0	27.1	33.0	58.0	8.5	951.9
Respiratory								
Low SDI	10.0	31.0	38.0	38.5	44.0	92.0	10.2	652.6
Middle SDI	26.0	49.0	57.0	58.7	67.0	125.0	13.8	777.2
High SDI	11.0	28.0	33.0	33.5	39.0	74.0	8.6	1066.5

[a] Death and hospitalization rates per 100,000 people were stratified by three levels of SDI for all of Hong Kong in 2001. SDI indicates social deprivation index.

APPENDIX H. Spearman Correlations and Partial Correlations Between Daily Pollutants for All Monitoring Stations, with Seasonal Adjustments

	Spearman Correlation				Partial Correlation[a]			
	NO_2	SO_2	PM_{10}	O_3	NO_2	SO_2	PM_{10}	O_3
NO_2	1.00	0.33	0.83	0.52	1.00	0.58	0.65	0.37
SO_2	—	1.00	0.20	−0.09	—	1.00	0.36	−0.15
PM_{10}	—	—	1.00	0.63	—	—	1.00	0.46
O_3	—	—	—	1.00	—	—	—	1.00

[a] The partial correlation with seasonal corrections was calculated by Spearman correlation between the residuals. The residuals were derived using a model that adjusted for time trend, temperature, and RH, using the same spline as the core model, for mortality due to all natural causes and correlated between pairwise pollutants.

APPENDIX I. ER (%) of Mortality with Changes in Degrees of Freedom per 10-μg/m^3 Increase in Pollutant Concentrations at Lag 0–1 Day

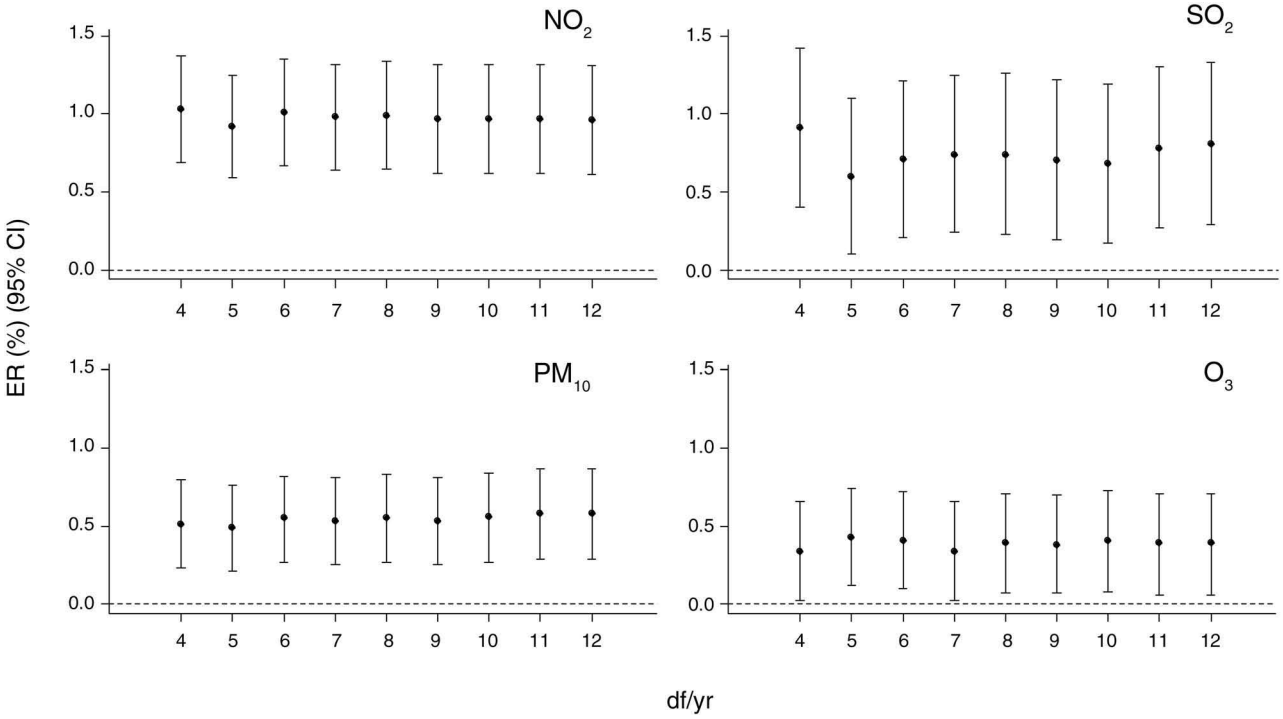

Figure I.1. A Forest plot showing mortality due to all natural causes, all ages, by pollutant.

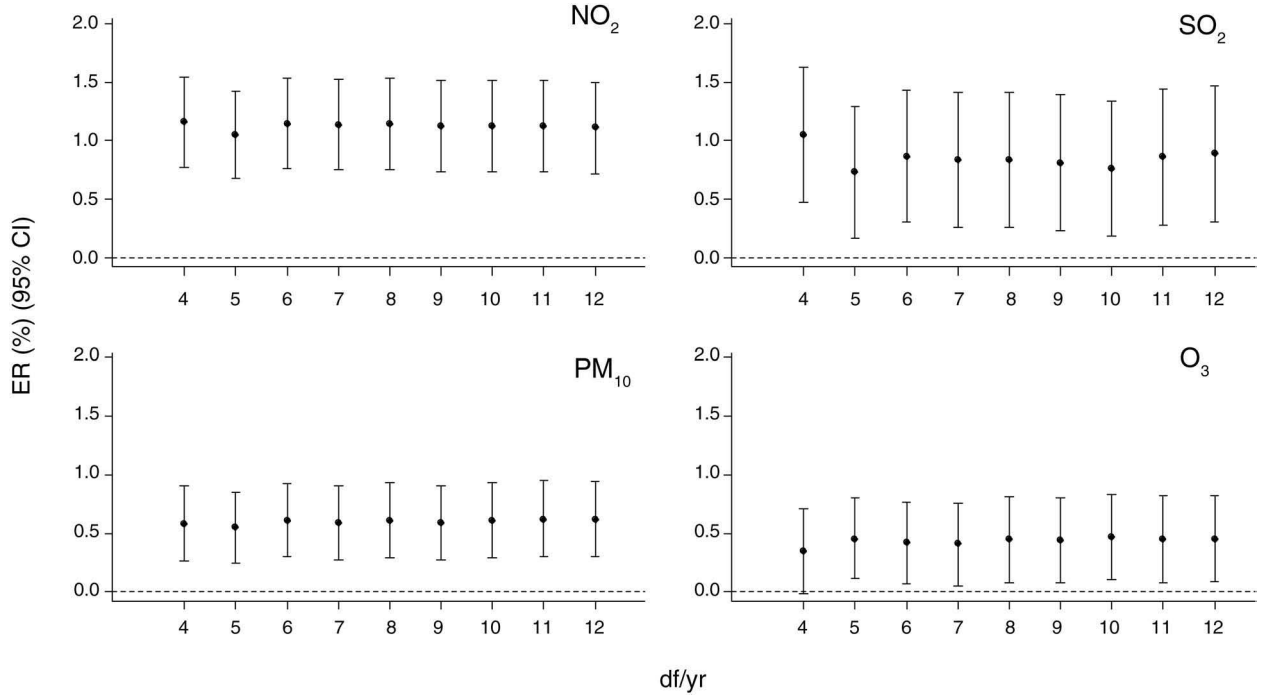

Figure I.2. A Forest plot showing mortality due to all natural causes, age 65+.

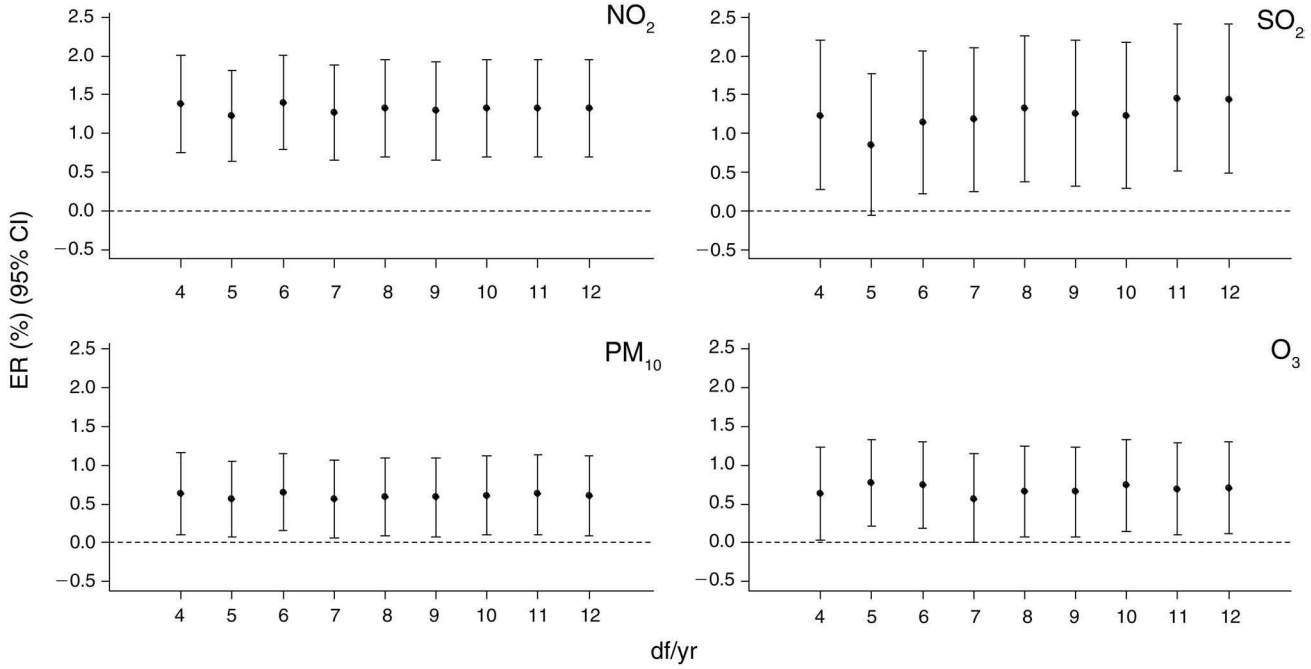

Figure I.3. A Forest plot showing cardiovascular-related mortality, all ages.

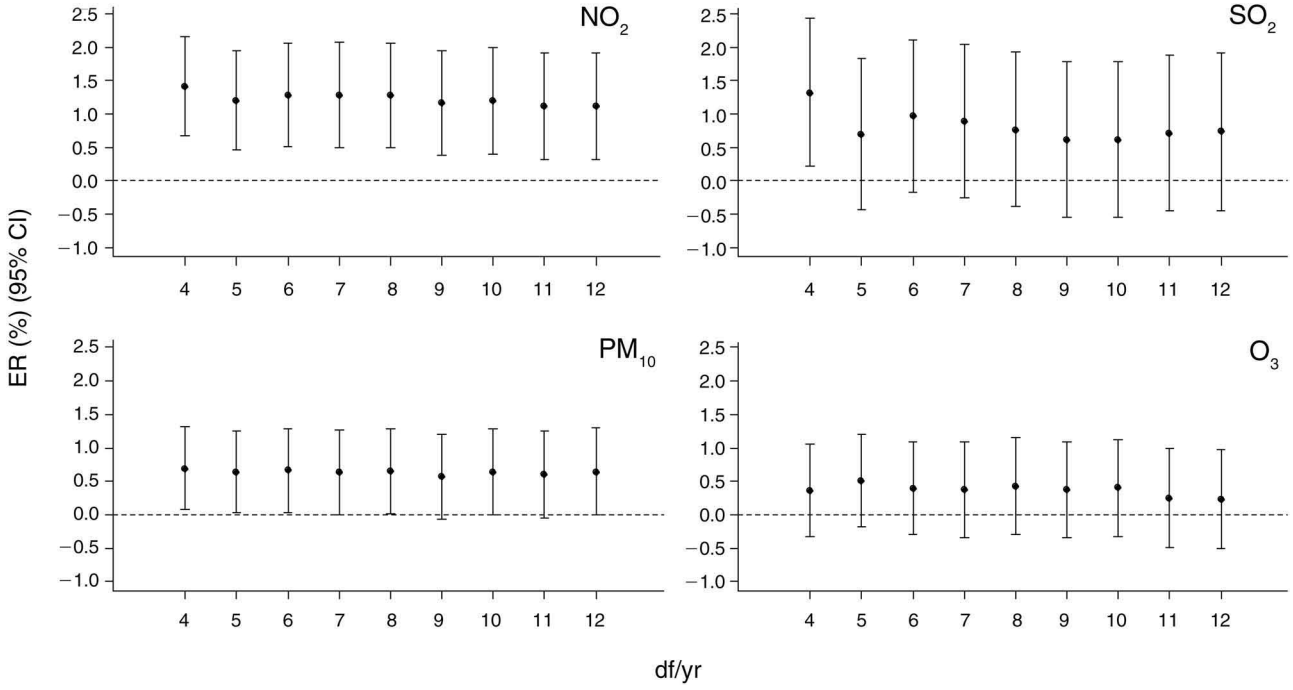

Figure I.4. A Forest plot showing respiratory-related mortality, all ages.

APPENDIX J. ER (%) of Hospitalization with Changes in Degrees of Freedom per 10-μg/m^3 Increase in Pollutant Concentrations at Lag 0–1 Day

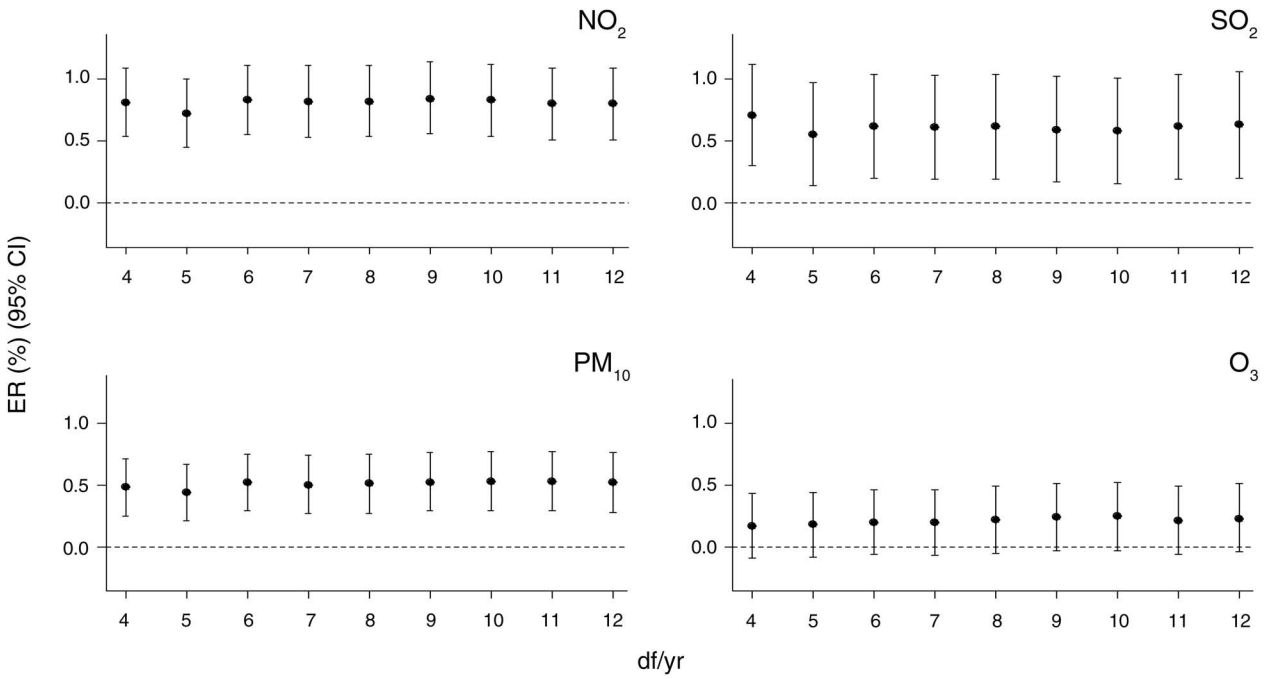

Figure J.1. A Forest plot showing cardiovascular-related hospitalization, all ages, M + F, by pollutant.

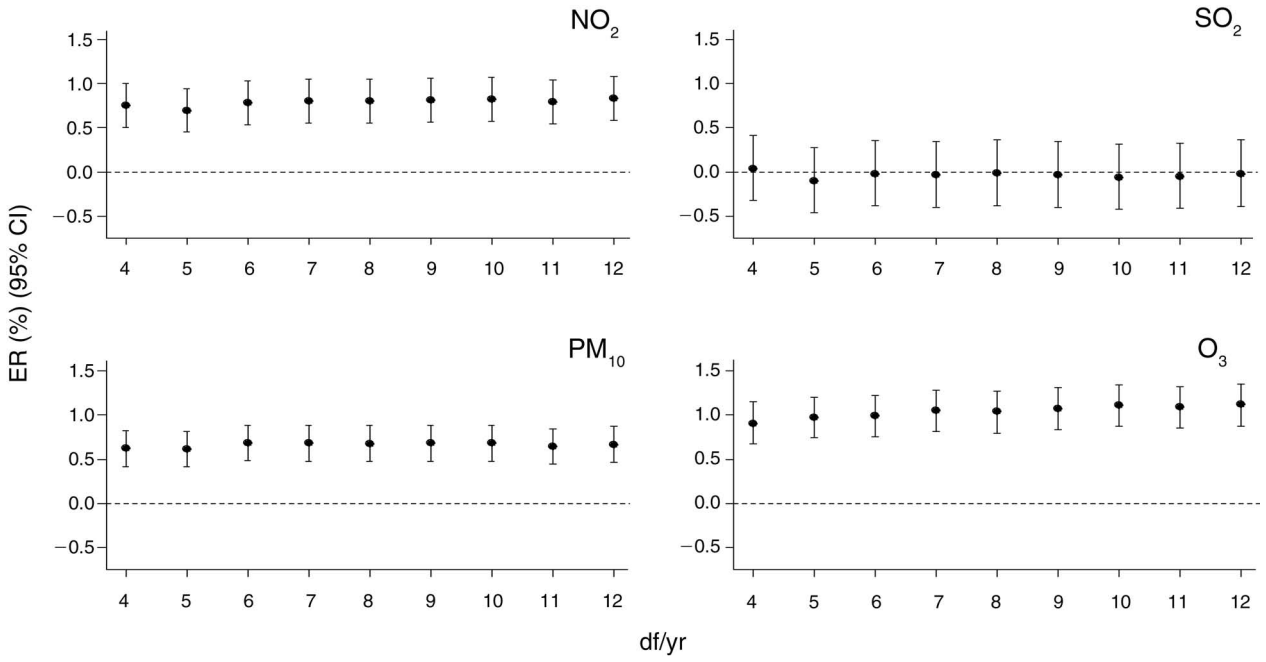

Figure J.2. A Forest plot showing respiratory-related hospitalization, all ages, M + F, by pollutant.

APPENDIX K. Summary Tables of ER (%) of Mortality per 10-μg/m^3 Increase in Concentration of Pollutants by Cause of Mortality and Pollutants, with Different Lags

Table K.1. ER (%) of Mortality Due to All Causes per 10-μg/m^3 Increase in Concentration of Pollutants, by Pollutant

Cause of Death / Lag	NO_2		SO_2		PM_{10}		O_3	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
All Natural Causes, All Ages, M + F								
0	0.81	(0.52 to 1.11)	0.69	(0.26 to 1.13)	0.39	(0.13 to 0.64)	0.18	(−0.11 to 0.47)
1	0.77	(0.47 to 1.06)	0.57	(0.15 to 1.00)	0.37	(0.14 to 0.61)	0.28	(0.03 to 0.54)
2	0.31	(0.02 to 0.61)	0.04	(−0.38 to 0.45)	0.16	(−0.07 to 0.39)	0.24	(0.00 to 0.49)
3	0.07	(−0.22 to 0.36)	−0.16	(−0.57 to 0.26)	−0.04	(−0.26 to 0.19)	0.15	(−0.09 to 0.39)
4	−0.20	(−0.49 to 0.09)	−0.28	(−0.69 to 0.13)	0.05	(−0.18 to 0.28)	−0.02	(−0.25 to 0.22)
0–1	1.03	(0.69 to 1.37)	0.91	(0.40 to 1.42)	0.51	(0.23 to 0.80)	0.34	(0.02 to 0.66)
0–4	0.72	(0.29 to 1.15)	0.42	(−0.28 to 1.11)	0.37	(0.03 to 0.72)	0.37	(0.01 to 0.74)
All Natural Causes, 65+, M + F								
0	0.94	(0.60 to 1.28)	0.88	(0.39 to 1.37)	0.47	(0.19 to 0.76)	0.21	(−0.12 to 0.53)
1	0.83	(0.50 to 1.17)	0.58	(0.10 to 1.06)	0.39	(0.12 to 0.66)	0.27	(−0.02 to 0.56)
2	0.37	(0.04 to 0.70)	0.07	(−0.41 to 0.54)	0.19	(−0.07 to 0.45)	0.34	(0.06 to 0.61)
3	0.11	(−0.22 to 0.44)	−0.09	(−0.56 to 0.38)	0.08	(−0.18 to 0.34)	0.28	(0.01 to 0.55)
4	−0.15	(−0.48 to 0.17)	−0.22	(−0.68 to 0.25)	0.16	(−0.09 to 0.42)	−0.03	(−0.29 to 0.24)
0–1	1.16	(0.77 to 1.54)	1.05	(0.47 to 1.63)	0.58	(0.26 to 0.91)	0.35	(−0.02 to 0.71)
0–4	0.87	(0.38 to 1.36)	0.61	(−0.17 to 1.41)	0.53	(0.14 to 0.91)	0.47	(0.06 to 0.89)

Table K.2. ER (%) of Cardiovascular- and Respiratory-Related Mortality per 10-μg/m^3 Increase in Concentration of Pollutants, by Pollutant

Cause of Death / Lag	NO_2		SO_2		PM_{10}		O_3	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Cardiovascular, All Ages, M + F								
0	1.13	(0.58 to 1.68)	0.96	(0.15 to 1.77)	0.43	(−0.04 to 0.90)	0.40	(−0.13 to 0.94)
1	0.98	(0.44 to 1.54)	0.75	(−0.04 to 1.55)	0.50	(0.06 to 0.94)	0.48	(0.00 to 0.96)
2	0.50	(−0.04 to 1.04)	0.13	(−0.65 to 0.91)	0.30	(−0.12 to 0.73)	0.57	(0.12 to 1.03)
3	0.01	(−0.53 to 0.54)	0.07	(−0.70 to 0.85)	0.02	(−0.40 to 0.45)	0.34	(−0.11 to 0.79)
4	−0.21	(−0.74 to 0.32)	−0.31	(−1.08 to 0.47)	0.20	(−0.21 to 0.62)	−0.14	(−0.58 to 0.30)
0–1	1.38	(0.75 to 2.01)	1.23	(0.27 to 2.21)	0.63	(0.11 to 1.16)	0.63	(0.04 to 1.23)
0–4	0.97	(0.18 to 1.77)	0.81	(−0.50 to 2.13)	0.60	(−0.03 to 1.23)	0.71	(0.03 to 1.40)
Respiratory, All Ages, M + F								
0	1.14	(0.49 to 1.80)	0.99	(0.06 to 1.93)	0.35	(−0.20 to 0.90)	0.12	(−0.50 to 0.74)
1	1.02	(0.38 to 1.67)	0.84	(−0.07 to 1.76)	0.65	(0.14 to 1.16)	0.34	(−0.21 to 0.89)
2	0.87	(0.24 to 1.50)	0.66	(−0.23 to 1.56)	0.82	(0.32 to 1.31)	0.72	(0.20 to 1.24)
3	0.55	(−0.08 to 1.18)	0.24	(−0.65 to 1.14)	0.46	(−0.03 to 0.96)	0.57	(0.06 to 1.09)
4	0.04	(−0.59 to 0.67)	−0.20	(−1.09 to 0.70)	0.46	(−0.03 to 0.95)	0.37	(−0.14 to 0.88)
0–1	1.41	(0.67 to 2.15)	1.31	(0.21 to 2.43)	0.69	(0.08 to 1.31)	0.36	(−0.33 to 1.05)
0–4	1.48	(0.55 to 2.42)	1.28	(−0.22 to 2.81)	1.17	(0.44 to 1.91)	1.01	(0.21 to 1.80)

Table K.3. ER (%) of Mortality Due to Accidental and Non-Cardiopulmonary Causes (Controls) per 10-μg/m^3 Increase in Concentration of Pollutants, by Pollutant

Cause of Death / Lag	NO_2		SO_2		PM_{10}		O_3	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Accidental, All Ages, M + F								
0	−0.37	(−1.61 to 0.88)	−0.12	(−1.85 to 1.65)	0.17	(−0.88 to 1.24)	−0.55	(−1.71 to 0.62)
1	−0.36	(−1.58 to 0.88)	−0.96	(−2.67 to 0.78)	−0.46	(−1.45 to 0.54)	−0.64	(−1.67 to 0.41)
2	−0.46	(−1.67 to 0.75)	−0.62	(−2.31 to 1.09)	0.09	(−0.87 to 1.05)	0.06	(−0.92 to 1.05)
3	−0.09	(−1.28 to 1.12)	0.54	(−1.13 to 2.23)	0.74	(−0.21 to 1.68)	0.29	(−0.67 to 1.27)
4	0.39	(−0.79 to 1.59)	0.21	(−1.45 to 1.90)	0.27	(−0.66 to 1.22)	0.01	(−0.95 to 0.98)
0–1	−0.45	(−1.85 to 0.96)	−0.76	(−2.81 to 1.33)	−0.22	(−1.40 to 0.97)	−0.83	(−2.11 to 0.48)
0–4	−0.35	(−2.09 to 1.42)	−0.51	(−3.26 to 2.31)	0.38	(−1.03 to 1.80)	−0.20	(−1.67 to 1.30)
Non-Cardiopulmonary, All Ages, M + F								
0	0.68	(0.32 to 1.05)	0.54	(0.01 to 1.07)	0.47	(0.16 to 0.79)	0.18	(−0.17 to 0.54)
1	0.76	(0.39 to 1.12)	0.52	(0.00 to 1.04)	0.28	(−0.02 to 0.58)	0.19	(−0.13 to 0.50)
2	0.24	(−0.12 to 0.60)	−0.03	(−0.54 to 0.49)	−0.04	(−0.32 to 0.25)	0.05	(−0.25 to 0.35)
3	0.17	(−0.19 to 0.53)	−0.23	(−0.74 to 0.28)	−0.16	(−0.45 to 0.12)	−0.01	(−0.30 to 0.29)
4	−0.09	(−0.45 to 0.26)	−0.27	(−0.77 to 0.25)	−0.17	(−0.45 to 0.12)	−0.05	(−0.34 to 0.25)
0–1	0.94	(0.52 to 1.36)	0.75	(0.12 to 1.39)	0.50	(0.14 to 0.85)	0.26	(−0.13 to 0.66)
0–4	0.71	(0.19 to 1.24)	0.24	(−0.60 to 1.10)	0.12	(−0.30 to 0.55)	0.15	(−0.30 to 0.60)

APPENDIX L. Summary Tables of ER (%) of Hospitalization per 10-μg/m^3 Increase in Concentration of Pollutants by Outcome and Pollutants, with Different Lags

Table L.1. ER (%) of Cardiovascular-Related Hospitalization per 10-μg/m^3 Increase in Concentration of Pollutants by Outcome, Pollutant, and Sex, with Different Lags

Disease Group / Lag	NO_2		SO_2		PM_{10}		O_3	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Cardiovascular, All Ages, M + F								
0	1.07	(0.83 to 1.30)	1.20	(0.86 to 1.54)	0.64	(0.44 to 0.84)	−0.10	(−0.32 to 0.13)
1	0.50	(0.27 to 0.74)	0.17	(−0.18 to 0.51)	0.28	(0.09 to 0.47)	0.24	(0.04 to 0.45)
2	0.40	(0.17 to 0.63)	−0.31	(−0.65 to 0.03)	0.13	(−0.05 to 0.32)	0.14	(−0.05 to 0.34)
3	0.52	(0.30 to 0.74)	0.17	(−0.17 to 0.51)	0.28	(0.10 to 0.46)	0.02	(−0.17 to 0.20)
4	0.32	(0.09 to 0.54)	−0.14	(−0.48 to 0.20)	0.14	(−0.04 to 0.31)	0.03	(−0.15 to 0.22)
0–1	1.00	(0.73 to 1.26)	0.98	(0.57 to 1.39)	0.58	(0.36 to 0.80)	0.12	(−0.12 to 0.37)
0–4	1.04	(0.72 to 1.35)	0.53	(−0.02 to 1.08)	0.52	(0.26 to 0.77)	0.14	(−0.14 to 0.41)
Cardiovascular, All Ages, M								
0	0.83	(0.53 to 1.12)	0.89	(0.47 to 1.32)	0.52	(0.26 to 0.77)	−0.11	(−0.40 to 0.18)
1	0.16	(−0.13 to 0.46)	−0.10	(−0.52 to 0.33)	0.24	(0.00 to 0.48)	0.20	(−0.06 to 0.46)
2	0.20	(−0.10 to 0.49)	−0.35	(−0.77 to 0.07)	0.01	(−0.22 to 0.25)	0.08	(−0.17 to 0.32)
3	0.30	(0.01 to 0.59)	−0.02	(−0.44 to 0.39)	0.20	(−0.03 to 0.43)	0.08	(−0.15 to 0.32)
4	0.15	(−0.14 to 0.44)	−0.05	(−0.47 to 0.36)	0.09	(−0.14 to 0.32)	0.23	(−0.01 to 0.46)
0–1	0.65	(0.31 to 0.99)	0.57	(0.07 to 1.08)	0.49	(0.21 to 0.78)	0.09	(−0.23 to 0.42)
0–4	0.68	(0.25 to 1.10)	0.17	(−0.51 to 0.86)	0.42	(0.08 to 0.76)	0.23	(−0.13 to 0.60)
Cardiovascular, All Ages, F								
0	1.06	(0.77 to 1.35)	0.99	(0.57 to 1.41)	0.57	(0.32 to 0.82)	−0.03	(−0.32 to 0.25)
1	0.61	(0.32 to 0.91)	0.36	(−0.06 to 0.78)	0.23	(0.00 to 0.47)	0.33	(0.07 to 0.58)
2	0.30	(0.01 to 0.58)	−0.19	(−0.60 to 0.23)	0.13	(−0.10 to 0.36)	0.30	(0.06 to 0.54)
3	0.43	(0.15 to 0.71)	0.45	(0.04 to 0.86)	0.21	(−0.02 to 0.43)	0.03	(−0.20 to 0.27)
4	0.15	(−0.13 to 0.44)	−0.05	(−0.46 to 0.35)	0.00	(−0.22 to 0.23)	−0.07	(−0.30 to 0.16)
0–1	1.10	(0.76 to 1.43)	0.97	(0.47 to 1.47)	0.52	(0.24 to 0.81)	0.24	(−0.08 to 0.56)
0–4	1.03	(0.61 to 1.45)	0.77	(0.09 to 1.45)	0.45	(0.11 to 0.79)	0.25	(−0.11 to 0.61)

Table L.2. ER (%) of Respiratory-Related Hospitalization per 10-μg/m^3 Increase in Concentration of Pollutants by Outcome, Pollutant, and Sex, with Different Lags

Disease Group / Lag	NO_2		SO_2		PM_{10}		O_3	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Respiratory, All Ages, M + F								
0	0.82	(0.61 to 1.04)	0.48	(0.17 to 0.78)	0.54	(0.36 to 0.72)	0.36	(0.16 to 0.56)
1	0.29	(0.07 to 0.51)	−0.30	(−0.61 to 0.00)	0.36	(0.19 to 0.53)	0.74	(0.56 to 0.93)
2	0.14	(−0.07 to 0.36)	−0.28	(−0.58 to 0.02)	0.19	(0.03 to 0.36)	0.47	(0.30 to 0.65)
3	0.25	(0.04 to 0.46)	0.12	(−0.18 to 0.41)	0.15	(−0.01 to 0.32)	0.07	(−0.10 to 0.24)
4	0.24	(0.03 to 0.45)	0.29	(0.00 to 0.59)	0.19	(0.03 to 0.36)	−0.04	(−0.21 to 0.14)
0–1	0.75	(0.50 to 1.00)	0.13	(−0.24 to 0.50)	0.60	(0.40 to 0.80)	0.81	(0.58 to 1.04)
0–4	0.82	(0.50 to 1.15)	0.20	(−0.31 to 0.71)	0.61	(0.36 to 0.87)	0.68	(0.41 to 0.95)
Respiratory, All Ages, M								
0	0.69	(0.44 to 0.94)	0.41	(0.05 to 0.77)	0.52	(0.30 to 0.73)	0.34	(0.09 to 0.58)
1	0.20	(−0.05 to 0.46)	−0.40	(−0.75 to −0.04)	0.37	(0.17 to 0.58)	0.73	(0.52 to 0.95)
2	0.25	(0.00 to 0.49)	−0.35	(−0.70 to 0.01)	0.37	(0.17 to 0.56)	0.65	(0.44 to 0.85)
3	0.36	(0.12 to 0.60)	0.12	(−0.23 to 0.47)	0.30	(0.10 to 0.49)	0.27	(0.06 to 0.47)
4	0.25	(0.01 to 0.50)	0.26	(−0.09 to 0.61)	0.19	(0.00 to 0.38)	0.14	(−0.07 to 0.34)
0–1	0.59	(0.30 to 0.88)	0.00	(−0.43 to 0.44)	0.59	(0.35 to 0.83)	0.79	(0.52 to 1.06)
0–4	0.76	(0.39 to 1.12)	0.02	(−0.57 to 0.60)	0.74	(0.44 to 1.03)	0.93	(0.61 to 1.25)
Respiratory, All Ages, F								
0	0.80	(0.51 to 1.09)	0.41	(−0.01 to 0.83)	0.47	(0.23 to 0.72)	0.29	(0.01 to 0.58)
1	0.33	(0.04 to 0.62)	−0.42	(−0.83 to 0.00)	0.32	(0.09 to 0.56)	0.77	(0.52 to 1.03)
2	0.01	(−0.28 to 0.30)	−0.37	(−0.78 to 0.04)	0.01	(−0.22 to 0.24)	0.36	(0.11 to 0.60)
3	0.07	(−0.21 to 0.36)	−0.04	(−0.45 to 0.37)	−0.02	(−0.24 to 0.21)	−0.07	(−0.31 to 0.17)
4	0.04	(−0.24 to 0.32)	0.12	(−0.28 to 0.53)	0.10	(−0.12 to 0.32)	−0.23	(−0.47 to 0.01)
0–1	0.75	(0.41 to 1.08)	−0.02	(−0.52 to 0.48)	0.53	(0.25 to 0.81)	0.80	(0.48 to 1.12)
0–4	0.53	(0.10 to 0.95)	−0.20	(−0.89 to 0.49)	0.36	(0.02 to 0.70)	0.46	(0.09 to 0.84)

APPENDIX M. Additional Temperature Splines at Lag 1–2 Days and Lag 3–7 Days: ER (%) of Mortality per 10-μg/m^3 Increase in Concentration of Pollutants

Cause of Death / Pollutant	Result from Core Model		Additional Temperature Adjustment (Lag 1–2)		Additional Temperature Adjustment (Lag 3–7)	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
All Natural Causes, All Ages						
NO_2	1.03	(0.69 to 1.37)	0.64	(0.30 to 0.98)	0.59	(0.26 to 0.93)
SO_2	0.91	(0.40 to 1.42)	0.81	(0.31 to 1.31)	0.66	(0.16 to 1.16)
PM_{10}	0.51	(0.23 to 0.80)	0.38	(0.11 to 0.66)	0.31	(0.03 to 0.59)
O_3	0.34	(0.02 to 0.66)	0.27	(−0.04 to 0.58)	0.26	(−0.05 to 0.57)
All Natural Causes, 65+						
NO_2	1.16	(0.77 to 1.54)	0.72	(0.34 to 1.11)	0.66	(0.28 to 1.05)
SO_2	1.05	(0.47 to 1.63)	0.95	(0.38 to 1.52)	0.81	(0.24 to 1.38)
PM_{10}	0.58	(0.26 to 0.91)	0.44	(0.13 to 0.76)	0.36	(0.04 to 0.67)
O_3	0.35	(−0.02 to 0.71)	0.12	(−0.15 to 0.38)	0.25	(0.11 to 0.38)
Cardiovascular						
NO_2	1.38	(0.75 to 2.01)	0.92	(0.28 to 1.57)	0.64	(−0.01 to 1.28)
SO_2	1.23	(0.27 to 2.21)	1.10	(0.15 to 2.07)	0.80	(−0.16 to 1.76)
PM_{10}	0.63	(0.11 to 1.16)	0.49	(−0.03 to 1.01)	0.32	(−0.20 to 0.84)
O_3	0.63	(0.04 to 1.23)	0.55	(−0.04 to 1.15)	0.50	(−0.09 to 1.09)
Respiratory						
NO_2	1.41	(0.67 to 2.15)	0.92	(0.18 to 1.68)	0.84	(0.09 to 1.60)
SO_2	1.31	(0.21 to 2.43)	1.12	(0.03 to 2.23)	0.85	(−0.25 to 1.96)
PM_{10}	0.69	(0.08 to 1.31)	0.49	(−0.12 to 1.10)	0.39	(−0.22 to 1.00)
O_3	0.36	(−0.33 to 1.05)	0.23	(−0.46 to 0.91)	0.27	(−0.42 to 0.95)

APPENDIX N. ER (%) of Daily Mortality per 10-μg/m^3 Change in Air Pollutants with an Average of Lag 0–1 Day, with and without Adjustment for Influenza Activity

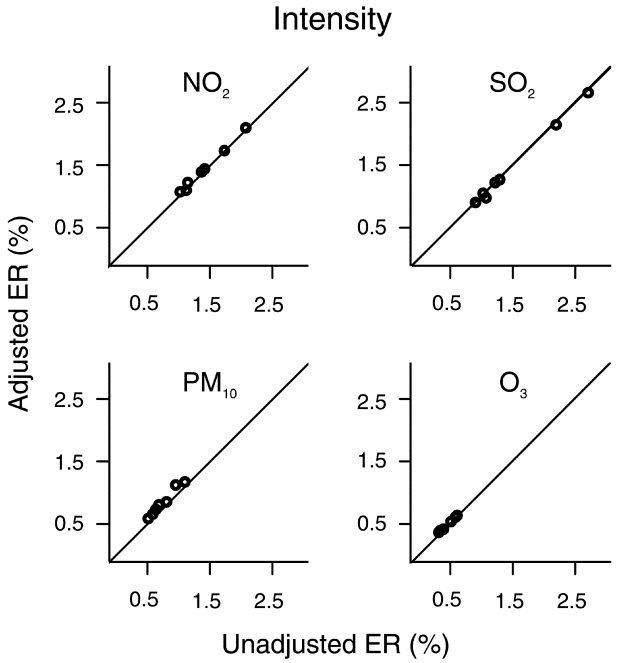

Figure N.1. ER in daily mortality per 10-μg/m^3 change in air pollutant concentration with an average of lag 0–1 day, with and without adjustment for influenza intensity for the following groups: all natural causes, cardiovascular, stroke, cardiac, respiratory, LRI, and COPD at all ages. The diagonal lines represent perfect correlation (1.0).

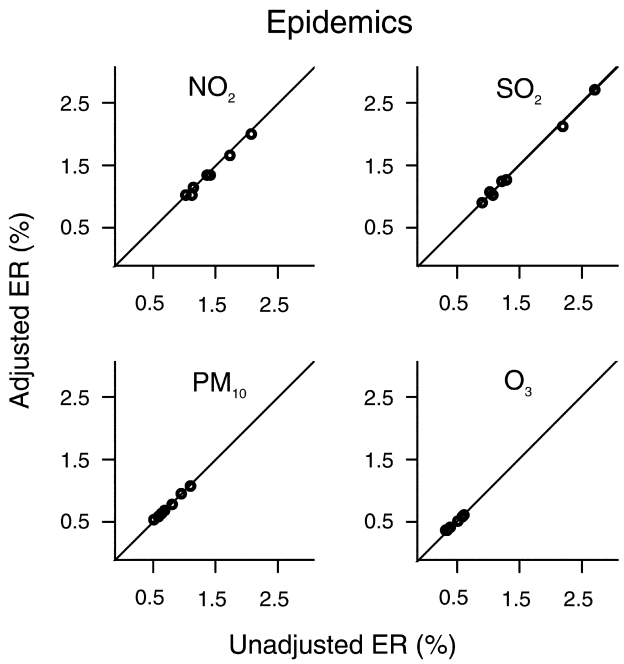

Figure N.2. ER in daily mortality per 10-μg/m^3 change in air pollutant concentration with an average of lag 0–1 day, with and without adjustment for influenza epidemics for the following groups: all natural causes, cardiovascular, stroke, cardiac, respiratory, LRI, and COPD at all ages. The diagonal lines represent perfect correlation (1.0).

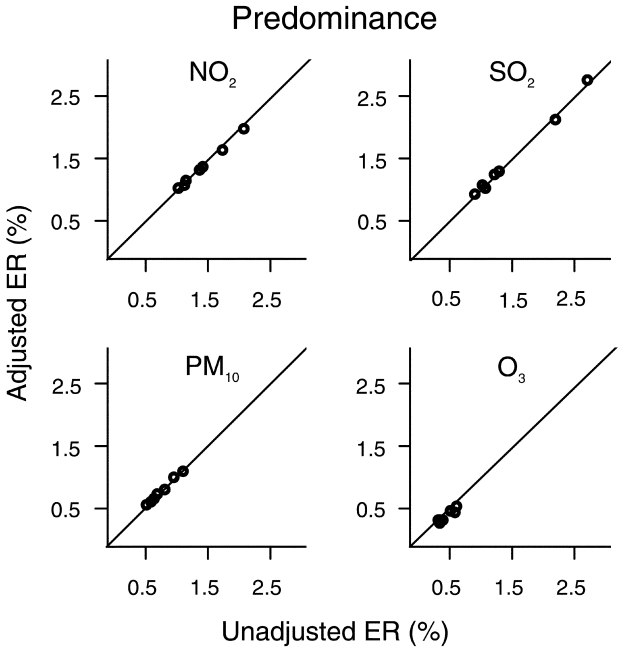

Figure N.3. ER in daily mortality per 10-μg/m^3 change in air pollutant concentration with an average of lag 0–1 day, with and without adjustment for influenza predominance for the following groups: all natural causes, cardiovascular, stroke, cardiac, respiratory, LRI, and COPD at all ages. The diagonal lines represent perfect correlation (1.0).

APPENDIX O. ER (%) of Daily Hospitalization from Changes in Air Pollutant Concentrations with an Average of Lag 0–1 Day, with and without Adjustment for Influenza Activity

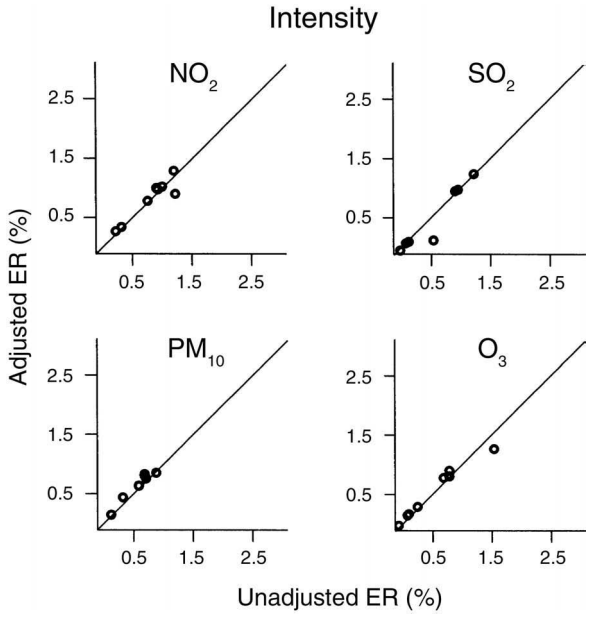

Figure O.1. ER in daily hospitalizations per 10-µg/m^3 change in air pollutant concentration at lag 0–1 day, with and without adjustment for influenza intensity for the following groups: cardiovascular, stroke, IHD, respiratory, ARD, ALRI, COPD, and asthma for all ages. The diagonal lines represent perfect correlation (1.0).

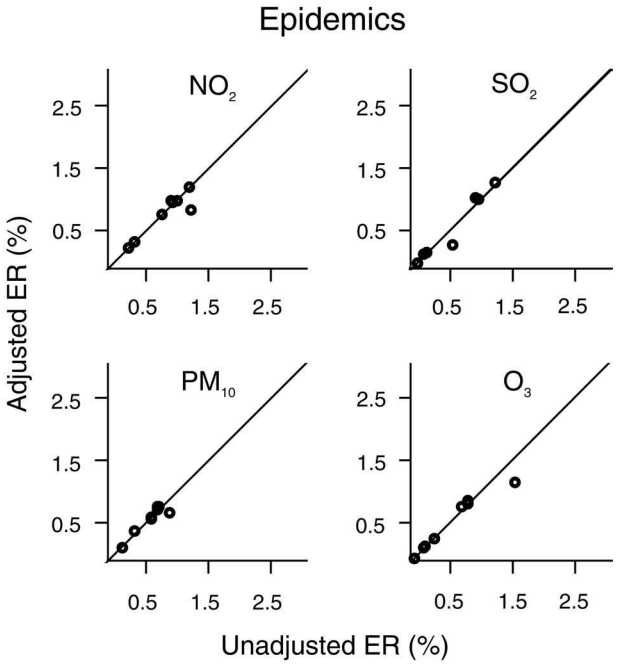

Figure O.2. ER in daily hospitalizations per 10-µg/m^3 change in air pollutant concentration at lag 0–1 day, with and without adjustment for influenza epidemics for the following groups: cardiovascular, stroke, IHD, respiratory, ARD, ALRI, COPD, and asthma for all ages. The diagonal lines represent perfect correlation (1.0).

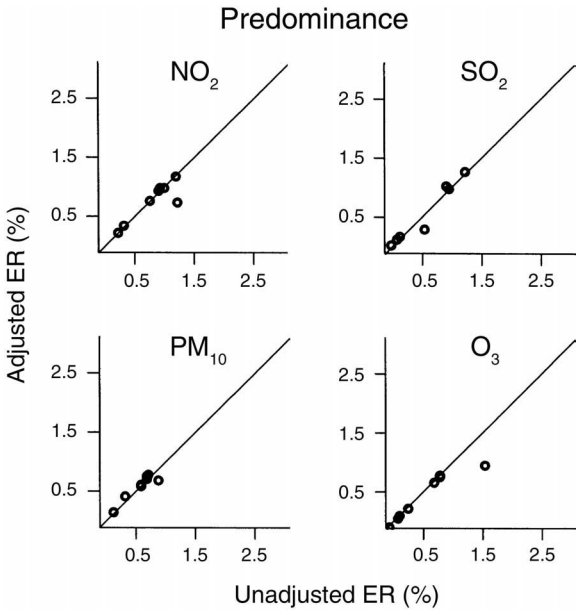

Figure O.3. ER in daily hospitalizations per 10-µg/m^3 change in air pollutant concentration with an average of lag 0–1 day, with and without adjustment for influenza predominance for the following groups: cardiovascular, stroke, IHD, respiratory, ARD, ALRI, COPD, and asthma for all ages. The diagonal lines represent perfect correlation (1.0).

APPENDIX P. ER (%) of Mortality Due to All Natural Causes per 10-μg/m^3 Increase in Pollutant Concentration by Three Levels of Social Deprivation at Different Lags for All Ages, Male and Female

Pollutant / Lag	Low SDI		Middle SDI		High SDI	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
NO_2						
0	0.72	(0.17 to 1.28)	1.24	(0.79 to 1.70)	0.77	(0.18 to 1.38)
1	0.55	(0.00 to 1.10)	1.15	(0.70 to 1.61)	1.27	(0.68 to 1.87)
2	0.29	(−0.24 to 0.83)	0.70	(0.25 to 1.15)	0.71	(0.12 to 1.29)
3	0.41	(−0.12 to 0.95)	0.44	(0.00 to 0.88)	0.30	(−0.28 to 0.88)
4	−0.20	(−0.73 to 0.33)	0.14	(−0.30 to 0.58)	−0.09	(−0.67 to 0.49)
SO_2						
0	0.76	(−0.04 to 1.57)	0.90	(0.24 to 1.56)	0.98	(0.11 to 1.86)
1	0.27	(−0.52 to 1.06)	0.67	(0.02 to 1.32)	1.52	(0.67 to 2.38)
2	0.28	(−0.49 to 1.06)	0.37	(−0.26 to 1.01)	0.40	(−0.44 to 1.24)
3	0.22	(−0.55 to 0.99)	0.19	(−0.44 to 0.83)	−0.35	(−1.18 to 0.49)
4	−0.66	(−1.43 to 0.11)	0.20	(−0.43 to 0.84)	−0.50	(−1.33 to 0.34)
PM_{10}						
0	0.38	(−0.09 to 0.86)	0.72	(0.33 to 1.11)	0.24	(−0.28 to 0.75)
1	0.41	(−0.03 to 0.86)	0.49	(0.13 to 0.86)	0.48	(0.01 to 0.97)
2	0.17	(−0.26 to 0.60)	0.35	(0.00 to 0.71)	0.33	(−0.14 to 0.79)
3	−0.09	(−0.51 to 0.34)	0.17	(−0.18 to 0.53)	0.00	(−0.46 to 0.46)
4	−0.12	(−0.54 to 0.31)	0.15	(−0.20 to 0.50)	−0.03	(−0.49 to 0.43)
O_3						
0	−0.16	(−0.69 to 0.38)	0.44	(0.00 to 0.88)	0.59	(0.01 to 1.17)
1	0.29	(−0.19 to 0.77)	0.53	(0.14 to 0.93)	0.13	(−0.39 to 0.65)
2	0.29	(−0.16 to 0.74)	0.27	(−0.10 to 0.64)	0.31	(−0.18 to 0.81)
3	0.09	(−0.36 to 0.53)	0.21	(−0.16 to 0.57)	0.29	(−0.20 to 0.77)
4	−0.09	(−0.53 to 0.35)	0.05	(−0.31 to 0.42)	0.07	(−0.41 to 0.55)

APPENDIX Q. ER (%) of Cardiovascular-Related Mortality per 10-μg/m^3 Increase in Pollutant Concentration by Three Levels of Social Deprivation at Different Lags for All Ages, Male and Female

Pollutant / Lag	Low SDI		Middle SDI		High SDI	
	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
NO_2						
0	0.94	(−0.12 to 2.02)	1.39	(0.60 to 2.18)	1.58	(0.51 to 2.66)
1	0.86	(−0.20 to 1.93)	1.13	(0.35 to 1.92)	2.24	(1.18 to 3.31)
2	0.44	(−0.60 to 1.48)	0.96	(0.20 to 1.73)	1.05	(0.01 to 2.10)
3	0.37	(−0.66 to 1.40)	0.57	(−0.18 to 1.34)	−0.18	(−1.22 to 0.86)
4	−0.44	(−1.47 to 0.59)	0.16	(−0.59 to 0.92)	0.09	(−0.94 to 1.13)
SO_2						
0	1.19	(−0.36 to 2.77)	0.82	(−0.33 to 1.99)	1.96	(0.39 to 3.55)
1	0.93	(−0.60 to 2.48)	0.35	(−0.78 to 1.50)	2.92	(1.39 to 4.47)
2	0.41	(−1.09 to 1.93)	0.40	(−0.71 to 1.52)	1.32	(−0.19 to 2.85)
3	0.31	(−1.18 to 1.82)	0.32	(−0.79 to 1.43)	0.11	(−1.39 to 1.64)
4	−0.72	(−2.21 to 0.79)	−0.24	(−1.34 to 0.88)	0.68	(−0.82 to 2.21)
PM_{10}						
0	0.15	(−0.76 to 1.06)	0.67	(0.00 to 1.34)	0.83	(−0.08 to 1.76)
1	0.65	(−0.20 to 1.50)	0.50	(−0.12 to 1.13)	0.89	(0.05 to 1.75)
2	0.26	(−0.56 to 1.09)	0.82	(0.22 to 1.43)	0.14	(−0.69 to 0.97)
3	−0.25	(−1.06 to 0.58)	0.68	(0.09 to 1.29)	−0.07	(−0.88 to 0.76)
4	0.03	(−0.78 to 0.84)	0.54	(−0.05 to 1.14)	0.05	(−0.76 to 0.87)
O_3						
0	0.27	(−0.77 to 1.32)	0.62	(−0.15 to 1.39)	0.70	(−0.35 to 1.76)
1	0.46	(−0.47 to 1.40)	0.72	(0.03 to 1.41)	0.30	(−0.64 to 1.25)
2	0.58	(−0.30 to 1.46)	0.61	(−0.04 to 1.26)	0.31	(−0.58 to 1.20)
3	0.57	(−0.29 to 1.44)	0.62	(−0.02 to 1.26)	−0.11	(−0.98 to 0.78)
4	−0.23	(−1.09 to 0.63)	0.09	(−0.54 to 0.73)	−0.45	(−1.31 to 0.43)

APPENDIX R. HEI Quality Assurance Statement

The conduct of this study was subjected to periodic, independent audits by a team from Hoover Consultants. This team consisted of auditors with experience in toxicology, epidemiology, and air quality data. The audits included in-process monitoring of study activities for conformance to the study protocols and examination of records and supporting data. The dates of each audit are listed in the table below with the phase of the study examined:

QUALITY ASSURANCE AUDITS

Date	Phase of Study
May 13–14 and 17, 2005	Records from this study were obtained by the investigators from external groups, and the audit did not extend beyond these records to the original data sources. The 5- and 10-Month Progress Reports were included in the audit. This study was conducted in accordance with two protocols: an individual protocol that included the unique features of the Hong Kong project and a combined protocol for the coordinated time-series analysis. The most highly resolved air pollution statistics in the 10-Month Report were the site-specific annual values in Appendix E, and the audit team regenerated a selection of these numbers from the hourly data files. Each individual site and month was in a separate Excel file, with formatting that was not identical between files. This made validation of the reported numbers a labor-intensive activity, so a subset of data was selected by convenience for verification. This subset included NO_2, SO_2, O_3, and RSP (PM_{10}) at the Central/Western monitoring site for 1996, RSP (PM_{10}) at Tai Po for 1999, and SO_2 at Yuen Long for 2002. All minimum, median, mean, and maximum values were verified when the investigators' stated data-completeness requirements (18 valid hours out of 24) were employed. Dropping these requirements led to values different from those reported in most cases, indicating that the reported procedure was followed by the investigators. Values for NO and NO_x were examined for internal consistency with NO_2. The U.S. EPA uses 24-hour filter sampling as the reference method for PM_{10}. The Hong Kong EPD makes such measurements every sixth day at each of their sites. Since the investigators have these data for 1996, they were compared to the corresponding 24-hour average concentrations from the TEOM. As indicated in Appendix B of the investigators' 5-Month Progress Report, the Air Services Laboratory used both point and long path measurements for NO_2, SO_2, and ozone. Most sites used point measurements, but two or three used long path, and individual sites have occasionally switched from one method to the other during the study period. The audit team received clarification from Peter Louie of the Air Services Laboratory on the considerations involved in such changes; he reported that the EPD had satisfied itself of the general comparability of the two measurements. The audit team reviewed the documentation of all the ad hoc project meetings, validation of computer programs, SOPs, and curriculum vitae for all study personnel. The 5- and 10-Month Progress Reports were compared and reviewed for changes in repeated tables. Hospital admission data on CD-ROM were examined for completeness and compared with report tables and published government reports. Values in Table 4 of the 10-Month Progress Report for 1999 (all natural mortality), 1997 (cardiac or heart disease), 1998 (tuberculosis), and 1996 (neoplasm excluding lung cancer) were compared to public census data from published reports. The listing of hospitals used in the analysis for the study period was verified in Appendix G of the 10-Month Report. The number of respiratory deaths in 1999 was traced through all transformations in the computer files to the values in Table 5 (10-Month Report). The Data Management System in Appendix G was reviewed (10-Month Report). For mortality data, Table 4 of the main body of the 10-Month Report was compared to Table 1 in Appendix C for all natural

causes. Totals were calculated based on the data in Table 1, and verified against the data files and against published reports. Table 4 values represent the total mortality after data cleaning. Information on tertiary planning units (TPUs) was obtained by the audit team and reviewed. TPU will be used as an indicator of socioeconomic status in the analysis of the Hong Kong data set.

April 10, 2008 A draft of the final study report was examined for internal consistency and conformance with the study proposal. Comments were provided to HEI via e-mail.

A written report of the May 2005 audit was provided to the Director of Science of the Health Effects Institute who transmitted these findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by experienced professionals in accordance with both study protocols. The final report appears to be an accurate representation of the study.

B. Kristin Hoover
Hoover Consultants

ABOUT THE AUTHORS

Chit-Ming Wong is an associate professor in the Department of Community Medicine at The University of Hong Kong. He obtained his B.Sc. in mathematics and management sciences from the University of Manchester Institute of Sciences and Technology, United Kingdom, in 1980 and his M.Sc. in medical statistics from the University of London School of Hygiene and Tropical Medicine in 1987. He earned his Ph.D. in biostatistics and epidemiology from The University of Hong Kong in 1993. He is currently the head of the biostatistics and environmental health research group in the Department of Medicine at The University of Hong Kong. His research interests are in statistical modeling of population-based spatial and temporal data for environmental health studies. He is the coordinator and principal investigator for several regional collaborative projects assessing the health impact of air pollution, influenza, and government air quality intervention.

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J.S.M. Peiris is a chair professor of the Department of Microbiology at The University of Hong Kong and is chief of virology at Queen Mary Hospital, Hong Kong. He received his undergraduate medical training at the University of Peradeniya, Sri Lanka, in 1972. He obtained his D.Phil. in virology at the University of Oxford, United Kingdom, in 1981. He is a fellow of the Royal College of Pathologists, United Kingdom; the College of Pathologists, Hong Kong; and the Hong Kong Academy of Medicine. He was elected a fellow of the Royal Society, United Kingdom. His recent research interests have been focused on the ecology, epidemiology, clinical disease burden, evolution, and pathogenesis of animal and human influenza. Working together with relevant government departments and other colleagues at The University of Hong Kong, he contributed to the efforts that resulted in Hong Kong being protected from the current wave of avian flu (H5N1) sweeping the region. In March 2003, he played a key role in the discovery that a novel coronavirus was the etiologic agent of severe acute respiratory syndrome (SARS). He continues to have a strong interest in viral diseases affecting humans with an emphasis on respiratory viral diseases. He has contributed to quantifying the impact of influenza on hospitalization and mortality. Previous research interests have included the pathogenesis and epidemiology of arboviruses and herpesviruses.

G. Neil Thomas is a reader at the University of Birmingham, United Kingdom. He was formerly an assistant professor in the Department of Community Medicine at The University of Hong Kong. He completed his Ph.D. in the genetic epidemiology of hypertension in the Chinese University of Hong Kong in 1999. He is a founding member of the Hong Kong Atherosclerosis Society (council member). His research predominantly focuses on vascular disease and the metabolic syndrome cluster of obesity, Type 2 diabetes, hypertension, dyslipidemia, and associated vascular disease. His multidisciplinary approach to these investigations ranges from biochemical and genetic epidemiology to prevention and treatment interventions.

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Anthony J. Hedley has been the chair professor of the Department of Community Medicine at The University of Hong Kong since 1988. He was head of the department from 1988 to 2000. He was formerly professor of public health in the University of Glasgow from 1983 to 1988. He attended medical school at Aberdeen (1959–65) and Edinburgh (1972–73) Universities. In 1964 he was a Nuffield Scholar in Tropical Medicine in the Fiji Islands based at the Fiji School of Medicine. After training in internal medicine in 1972, he obtained an M.D. by research and M.R.C.P. (United Kingdom) in 1973 and an M.F.P.H. by examination from the Royal College of Physicians, United Kingdom, in 1975. He was chairman of the Hong Kong Health Services Research Committee Expert Subcommittee on Grant Applications from 1993 to 2003. His main research and public health advocacy interests in recent years have been in the field of environmental health, including outdoor and indoor air pollution, and the prevention of disease caused by tobacco. He was a member and later chairman of the Hong Kong Council on Smoking and Health from 1994 to 2002. In 1999 he received a WHO medal for outstanding contributions to public health.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Wong CM, Ou CQ, Chan KP, Chau YK, Thach TQ, Yang L, Chung RYN, Thomas GN, Peiris JSM, Wong TW, Hedley AJ, Lam TH. 2008. The effects of air pollution on mortality in socially deprived urban areas in Hong Kong, China. Environ Health Perspect 116:1189–1194.

Wong CM, Vichit-Vadakan N, Kan HD, Qian ZM, and the PAPA Project Teams. 2008. Public Health and Air Pollution in Asia (PAPA): A multicity study of short-term effects of air pollution on mortality. Environ Health Perspect 116: 1195–1202.

Wong CM, Yang L, Thach TQ, Chau PYK, Chan KP, Thomas GN, Lam TH, Wong TW, Hedley AJ, Peiris JSM. 2009. Modification by influenza on health effects of air pollution in Hong Kong. Environ Health Perspect 117:248–253.

ABBREVIATIONS AND OTHER TERMS

ALRI	acute lower respiratory infection
ARD	acute respiratory disease
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
df	degree of freedom
DH	Department of Health, Hong Kong
ER	excess risk
F	female
HEI	Health Effects Institute
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases*, 9th revision
ICD-10	*International Classification of Diseases*, 10th revision
IHD	ischemic heart disease
influenza A+B	influenza A and B viruses
LRI	lower respiratory infection
M	male
NO_2	nitrogen dioxide
O_3	ozone
PAPA	Public Health and Air Pollution in Asia program
PACF	partial auto-correlation function
PM_{10}	particulate matter ≤ 10 μm in aerodynamic diameter
QMH	Queen Mary Hospital
RD	respiratory disease
RH	relative humidity
RSV	respiratory syncytial virus
SDI	social deprivation index
SO_2	sulfur dioxide
SOP	standard operating procedure
TEOM	tapered element oscillating microbalance
TPU	tertiary planning unit
WHO	World Health Organization

Research Report 154, Part 4. *Interaction Between Air Pollution and Respiratory Viruses: Time-Series Study of Daily Mortality and Hospital Admissions in Hong Kong*, C-M. Wong et al.

INTRODUCTION

The study by Chit-Ming Wong from The University of Hong Kong and colleagues, titled *Interaction Between Air Pollution and Respiratory Viruses: Time-Series Study of Daily Mortality and Hospital Admissions in Hong Kong*, was conducted as part of a coordinated suite of time-series studies of the health effects of short-term exposure to air pollution in major Asian cities. These studies are a major component of HEI's Public Health and Air Pollution in Asia (PAPA*) program. Information on the origins, objectives, and scope of the PAPA program are provided in the Preface to this report. Background information on the demographic, health, and environmental conditions in Asia, and a brief review of previous epidemiologic research on the health effects of air pollution in Hong Kong are presented in the Overview.

OBJECTIVES AND SPECIFIC AIMS OF THE STUDY

Dr. Wong and colleagues proposed to study associations between levels of air pollutants and the risk of mortality and hospitalization in Hong Kong. They also proposed to investigate the possible effect on mortality and hospital admissions of interaction between air pollution and (a) influenza and (b) socioeconomic status.

The specific aims of the study were to assess the following:

1. The short-term effects of air pollution on mortality and hospital admissions;
2. The health impact of influenza activity with a view to addressing the validity of three measures of influenza activity based on virologic data;
3. The confounding effects of influenza on the health effects of air pollution;
4. The interaction between the effects on health of air pollution and influenza activity; and
5. The interaction between the effects on health of air pollution and social deprivation at the neighborhood level.

DATA SOURCES

The data were derived from a combination of publicly available administrative databases and clinical databases maintained by health care facilities.

HEALTH DATA

Mortality Data

Daily mortality data spanning the 7-year period from January 1996 to December 2002 were extracted from the Hong Kong Census and Statistics Department mortality records, which included age, sex, date of death, residence (in one of the tertiary planning units [TPUs] into which Hong Kong is divided), and the underlying cause of death. The cause of death was indicated by coding from the *International Classification of Disease, Revision 9* (ICD-9) in the years 1996–1999 and *Revision 10* (ICD-10) in the years 2000–2002. The ICD codes and categories of cause of death are displayed in Table 1 of the Investigators' Report.

Hospital Admissions Data

The hospital admissions data were extracted from the medical records of the 19 acute and general hospitals of Hong Kong's Hospital Authority for the 7-year period of

Dr. Chit-Ming Wong's 2-year study, "Interaction Between Air Pollution and Respiratory Viruses: Time-Series Study of Daily Mortality and Hospital Admissions in Hong Kong", began in May 2004. Total expenditures were $149,826. The draft Investigators' Report from Wong and colleagues was received for review in September 2006. A revised report, received in November 2007, was accepted for publication in December 2007. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Commentary.

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*A list of abbreviations and other terms appears at the end of the Investigators' Report.

January 1996 to December 2002. Extracted information included the date of admission, sex, age, district of residence, and discharge diagnosis defined by the appropriate ICD-9 code. The disease categories considered and the corresponding ICD-9 codes are shown in Table 2 of the Investigators' Report.

Influenza Data

Weekly counts of positive isolates of influenza A and B viruses (*influenza A+B*), as well as the total specimens tested, were obtained from the virology laboratory of Queen Mary Hospital in Hong Kong. From these data, the investigators defined three measures of influenza activity:

1. *Influenza intensity:* the weekly proportion of positive isolates of influenza in the total number of specimens received for diagnostic tests;
2. *Influenza epidemic:* a period when the weekly count of positive influenza isolates was ≥ 4% of the annual total number of positive isolates in 2 or more consecutive weeks. This would be at least double the expected percentage in any week (based on the assumption that in one year, each week would have the same number of cases — i.e., < 2% of the annual total number of positive isolates); and
3. *Influenza predominance:* a period of influenza epidemic when the weekly counts of respiratory syncytial virus (RSV) were < 2% (of the weekly expected value) for 2 or more consecutive weeks. The investigators adjusted influenza effects for RSV because RSV is also a major cause of hospitalization, particularly in the very young and elderly, and produces symptoms similar to those of influenza infection. Wong and colleagues obtained weekly data on RSV isolates from the same hospital that collected the influenza data.

EXPOSURE AND OTHER COVARIATE DATA

Air Pollution Data

Air pollution data were obtained from the Hong Kong Environmental Protection Department. Hourly measurements of ozone (O_3), nitrogen dioxide (NO_2), particulate matter (PM) with an aerodynamic diameter ≤ 10 μm (PM_{10}) and sulfur dioxide (SO_2) were obtained for eight stations. The hourly data were averaged to produce 8-hour maximum concentrations of O_3, and 24-hour average concentrations for the other pollutants (Commentary Table 1). One site was not used in the O_3 analysis because the collected data did not meet the data criteria set for the PAPA studies (see the Integrated Discussion in Part 5 of this volume). Daily data that met the PAPA criteria and were deemed acceptable were averaged using centering to obtain values for use in the air quality–health association analyses. The use of centering is discussed further in the Integrated Discussion.

Commentary Table 1. Mean and Maximum Pollutant Concentrations,[a] Temperature, and Relative Humidity in Hong Kong During Study Period

	Mean (SD)	Maximum
Concentration (μg/m^3)		
NO_2	58.7 (20.0)	168.0
SO_2	17.8 (12.1)	109.4
PM_{10}	51.6 (25.3)	188.5
O_3	36.9 (23.0)	196.6
Meteorologic Variables		
Temperature (°C)	23.7 (4.9)	33.8
RH (%)	77.9 (10.0)	97.0

[a] 24-hour for NO_2, SO_2, and PM_{10}; 8-hour for O_3.

Meteorologic Data

Daily meteorologic data were obtained from the Hong Kong Observatory for the study period. The data included daily mean temperature and daily mean relative humidity (RH) (Commentary Table 1).

Social Deprivation Index

The social deprivation index (SDI), an indicator of socioeconomic deprivation, was calculated at the TPU level. TPUs are the smallest census units. The SDI was calculated for 209 of 276 total TPUs in Hong Kong as the average of the proportions of residents who were unemployed, lived in households with income < U.S. $250 per month, had no formal education, lived in single-person households, had never married, and had a subtenant living arrangement. The TPUs were then grouped into three socioeconomic categories — low, middle, and high — based on the tertiles of the SDI.

DATA ANALYSIS

Statistical Model

Core statistical models were developed according to the Common Protocol adopted by all the PAPA investigators (and found at the end of this volume). A generalized additive modeling approach was used to obtain the excess risk (ER), assuming a Poisson distribution, of daily mortality or hospital admissions associated with daily increases in

pollutant levels. The investigators used quasi-likelihood methods to model the association between pollutants and daily mortality counts or hospitalization rates, with exposure lagged variously from 0 to 4 days; a dummy variable was included for public holidays. Because the daily variations in hospital admissions were greater than the variations in mortality, models for hospital admissions included more degrees of freedom (df) in the spline smoothing functions of time trend, temperature, and RH. Only natural splines were used for the hospitalization data because the investigators' preliminary data indicated similar findings for mortality using both natural and penalized splines. All results are presented as ER per 10-μg/m^3 increase in pollutant concentration, calculated from the relative risk (RR) as follows: ER = (RR − 1) × 100.

Building on the core model, the investigators developed specific models to assess the main effects of air pollution, control for confounding by influenza, and assess modification of the ER of air pollution on daily mortality and hospitalization rates by influenza and socioeconomic status.

- **Model 1: Main Effects of Air Pollution.** Concentrations of the four pollutants were added to the core model as linear terms in separate (single-pollutant) models. The investigators calculated the ER from air pollution for average concentrations for lag 0–1 day (the average of a same-day and 1-day lag).
- **Model 2: Main Effects of Influenza.** The three influenza measures were added to the core model individually as linear terms with adjustments for the weekly proportions of RSV positive isolates.
- **Model 3: Confounding Effect of Influenza and Other Respiratory Viruses on the Health Effects of Air Pollution.** Model 1 was adjusted separately for each of the three measures of influenza and for weekly proportions of the positive isolates of RSV in the specimen total. Confounding was considered to exist if there was > 0.1% change in the magnitude of the ERs.
- **Model 4: Modifying Effect of Influenza on the Association Between Air Pollution and Health Outcomes.** Statistical interaction terms — defined as the product of the pollutants and respective influenza measures — were added to Model 3.
- **Model 5: Modifying Effect of Socioeconomic Status on the Association Between Air Pollutant Levels and Health Outcomes.** Model 1 was fit to strata defined by tertiles of the SDI.

Sensitivity Analyses

The following sensitivity analyses were performed to assess the robustness of the air pollution effect estimates based on Model 1 to alternative analytic approaches and assumptions:

- *Variation in the degree of control for time-varying confounders, time trend, and seasonality:* Degrees of freedom for time trend were varied from 4 to 12;
- *Variation in lag structure:* Different lag structures were assessed, including single-day air pollution exposure lags from day 0 to day 4 and multiday lags including lag 0–1 and lag 0–4 days;
- *Enhanced control for the effects of temperature:* Additional smoothers for temperature were included with an average of lag 1–2 days and 3–7 days;
- *Assessment of effects on control causes of death:* The effects of air pollution on accidental and nonaccidental non-cardiopulmonary deaths were estimated based on the assumption that these causes should be unaffected by air pollution; and
- *Test for linearity of concentration–response relation:* Concentration–response curves with a smoothing spline function (at 3 df) were generated for each pollutant. Formal tests of linearity based on the deviance between models with a nonlinear term of pollutants and models with a linear term of pollutants were conducted to detect significant departures from the assumption of linearity.

RESULTS

POLLUTANT LEVELS AND METEOROLOGIC INFORMATION

Commentary Table 1 summarizes the mean and maximum pollutant levels and meteorologic variables found during the study period. Hong Kong's climate is typical of a tropical, coastal location and is characterized by high average temperatures and high levels of humidity, with relatively less variation than in Wuhan and Shanghai (two of the other cities in the PAPA studies). The levels of SO_2, NO_2, and PM_{10} and the relatively low background median O_3 level suggest a strong influence of local combustion-related sources.

INFLUENZA-ASSOCIATED MORTALITY

Influenza was associated with cardio-respiratory mortality and hospital admissions at time scales ranging from 1 to multiple weeks. All three measures of influenza activity were associated with most respiratory and cardiovascular hospitalizations except for those due to stroke and asthma.

Commentary Table 2. Summary of Main Results: ER (%) of Mortality and Hospitalization per 10-μg/m^3 Increase in Average Concentration of Pollutants at Lag 0–1 Day for Entire Sample (All Ages), With and Without Adjustment for Influenza Intensity

	NO_2		SO_2		PM_{10}		O_3	
Outcome	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)	ER	(95% CI)
Mortality								
All natural causes	1.03	(0.69 to 1.37)	0.91	(0.40 to 1.42)	0.51	(0.23 to 0.80)	0.34	(0.02 to 0.66)
Adjusted for influenza intensity	1.06	(0.73 to 1.40)	0.88	(0.37 to 1.39)	0.58	(0.30 to 0.86)	0.36	(0.05 to 0.68)
Cardiovascular	1.38	(0.75 to 2.01)	1.23	(0.27 to 2.21)	0.63	(0.11 to 1.16)	0.63	(0.04 to 1.23)
Adjusted for influenza intensity	1.38	(0.76 to 2.01)	1.20	(0.24 to 2.17)	0.72	(0.20 to 1.24)	0.62	(0.03 to 1.21)
Respiratory	1.41	(0.67 to 2.15)	1.31	(0.21 to 2.43)	0.69	(0.08 to 1.31)	0.36	(−0.33 to 1.05)
Adjusted for influenza intensity	1.42	(0.68 to 2.16)	1.25	(0.14 to 2.37)	0.78	(0.17 to 1.39)	0.37	(−0.32 to 1.06)
Hospital Admissions								
Cardiovascular	1.00	(0.73 to 1.26)	0.98	(0.57 to 1.39)	0.58	(0.36 to 0.80)	0.12	(−0.12 to 0.37)
Adjusted for influenza intensity	1.02	(0.76 to 1.28)	0.96	(0.56 to 1.37)	0.62	(0.39 to 0.84)	0.15	(−0.09 to 0.40)
Respiratory	0.75	(0.50 to 1.00)	0.13	(−0.24 to 0.50)	0.60	(0.40 to 0.80)	0.81	(0.58 to 1.04)
Adjusted for influenza intensity	0.76	(0.52 to 1.01)	0.07	(−0.29 to 0.44)	0.61	(0.40 to 0.81)	0.80	(0.58 to 1.03)

Associations Between Individual Pollutants and Health Outcomes, and Adjustment for Influenza Intensity

The investigators' main findings based on lag 0–1 day are shown in Commentary Table 2. In summary, they reported that exposure to increased concentrations of individual air pollutants was associated with higher risks of mortality and hospitalization from cardio-respiratory disease. The investigators also reported that influenza activity, measured by any of the three parameters, did not confound the associations between any air pollutant and hospitalizations and mortality due to all natural causes or cardiovascular disease (Commentary Table 2); influenza did affect the magnitude of some associations between individual pollutants and respiratory causes of mortality (see Investigators' Report Table 15).

Modifying Effects of Influenza on Estimation of the Health Effects from Air Pollution

Although influenza activity did not confound the associations between any air pollutant and all-cause or cardiovascular hospitalizations and mortality, the investigators reported modification of the ER for some pollutants and hospitalization for some respiratory causes but generally not for cardiovascular disease (see Investigators' Report Tables 20–22).

EFFECTS OF SOCIAL DEPRIVATION ON HEALTH EFFECTS OF AIR POLLUTION

The investigators examined mortality (see Investigators' Report Table 23) and hospitalization (see Appendix G of the Investigators' Report) and found that residence in a neighborhood with a high SDI (low socioeconomic status) was associated with higher cardiovascular mortality, but not hospitalizations.

For all natural, cardiovascular-related, and respiratory-related causes of mortality, the largest effects of air pollutants were seen at lag 0 day and lag 1 day, and were comparable in the high, middle, and low SDI groups (Appendix P and Q). Investigators' Report Figure 10 also shows that the effects on mortality (at lag 0–1 day) of increases in NO_2, SO_2, PM_{10}, and O_3 were generally consistent among the three SDI groups. For hospital admissions, the investigators found little evidence to suggest that social deprivation influenced the effect of air pollution on rates of hospital admissions.

SENSITIVITY AND OTHER ANALYSES

Degree of Control for Time-Varying Confounders, Time Trend, and Seasonality

The investigators reported that for most mortality outcomes, the ERs for NO_2 and SO_2 were slightly higher (on average 0.05 and 0.19, respectively) using 4 df, but did not

change using 5 to 12 df. ERs for PM_{10} and O_3 were stable for 4 to 12 df. For cardiovascular- and respiratory-related hospitalization, the ERs associated with each pollutant using different degrees of freedom varied in a way similar to those for mortality (see Figures J.1 and J.2 in the Investigators' Report Appendix J).

Variation in Lag Structure

The investigators reported that for NO_2 and SO_2, the lag patterns for all mortality outcomes reported (all natural causes [all ages and 65+], cardiovascular, and respiratory) were similar, namely, the highest ERs were at lag days 0 and 1 and decreased successively through lag days 2, 3, and 4. They reported that PM_{10} did not display this pattern. The pattern for O_3 showed increases at lag days 1 and 2 (Investigators' Report Figure 4). The investigators reported that patterns for different single-day lags for cardiovascular- and respiratory-related hospitalization for each pollutant were similar to the pattern observed with mortality (Investigators' Report Figure 5).

Temperature For all mortality outcomes, adjusting for temperature at lag 1–2 or 3–7 days, in addition to lag 0 day, decreased the ER for all pollutants, though in general the changes were not enough remove the associations (see Appendix M in the Investigators' Report).

Control Causes of Death No associations were found for any pollutant with accidental mortality, but some positive associations with mortality due to non-cardiopulmonary (nonaccidental) causes were found (see Appendix K in the Investigators' Report).

Concentration–Response Curves Investigators' Report Figure 6 shows that the concentration–response curves for each pollutant and various mortality outcomes were similar but that the shape of the concentration–response curve was unique for each pollutant. Thus, for most mortality outcomes, the curve for NO_2 was concave, with its minimum at approximately 50 $\mu g/m^3$; the SO_2 curve was convex, with a larger confidence interval above 60 $\mu g/m^3$; the PM_{10} curve was roughly linear; and the O_3 curve was irregular but concave. For hospitalizations (data shown in Investigators' Report Figure 7), all pollutants showed some linear relation except O_3 for cardiovascular disease. The results of the concentration–response analysis agreed with the results of the test for nonlinearity (Investigators' Report Table 10).

HEI EVALUATION OF STUDY

The Review Committee assessed the quality of the data, the analytic design and methods, and the results reported by Dr. Wong and colleagues. The Committee then reviewed the investigators' conclusions regarding the effects of short-term exposure to air pollution on mortality and hospital admissions, and the extent to which these effects were modified by influenza activity and socioeconomic status.

ASSESSMENT OF HEALTH OUTCOMES

For the most part, Wong and colleagues used the same mortality and hospitalization outcome categories employed in time-series studies in other cities around the world (see Investigators' Report Tables 1–3). Because of both the extent of the time-series data available and the size of the city, however, the Hong Kong investigators had available for analysis a large number of daily deaths and hospitalizations: on average, there were 84 deaths from all natural causes and 474 hospitalizations for cardio-respiratory causes. This allowed them to make assessments of the effects on mortality and hospitalizations among age strata that were relatively more detailed and to define more narrowly the strata of cause of death or hospitalization diagnosis, as well as the "control" causes of death. For example, even a specific hospitalization diagnostic category such as asthma, for which there was a mean of 27 hospitalizations per day, had adequate power to detect pollutant effects. However, the categorization of cause of death was based on *underlying cause of death* from ICD codes, while the hospitalization categorization was based on *hospital discharge diagnosis*, potentially affecting the consistency of results when comparing the two.

MONITORING AND EXPOSURE ESTIMATION IN HONG KONG

Reliability of Monitoring Information

The available monitoring data provided a reliable basis for estimation of the health effects of short-term exposure. The Hong Kong air pollution monitoring network utilizes standard techniques, similar to those commonly used for routine monitoring in the United States, augmented in some locations with differential optical absorption spectroscopy, which provides measurements of NO_2, SO_2, and O_3. In the case of NO_2, measurements are not subject to potential interference from other oxidized nitrogen species, as is true for measurements made by more frequently used chemiluminescent monitors. In addition, differential optical absorption spectroscopy measures pollution over a larger area than other techniques.

The Hong Kong Environmental Protection Department uses traditional quality assurance/quality control procedures to verify the pollutant monitoring data. Pollutant data in Hong Kong were checked for completeness in order

to develop daily (or 8-hour maximum for O_3) measures and then centered and averaged, in keeping with the PAPA Common Protocol.

The investigators included data from multiple monitoring stations distributed around the area in order to provide calculated concentrations representative of the metropolitan area. The high correlations between pollutant measurements at different monitoring locations also serve to increase confidence in the reliability of the pollutant measures (see Investigators' Report Table 6). PM_{10} levels at different monitoring sites were highly correlated, with site-to-site Spearman correlations typically above 0.9, consistent with a highly uniform level of PM across the area. This most likely reflects either the secondary formation of PM or the presence of regionally transported pollution from elsewhere in the Pearl River Delta, as discussed in the Overview, or both. O_3 levels were similarly highly correlated (with Spearman correlations generally around 0.8; see Investigators' Report Table 6). The correlations were less consistently strong for NO_2 and SO_2, though still high, suggesting that similar pollutant sources and effects from the regional transport of air pollutants were measured at all the different monitors in Hong Kong. Taken together, the strong correlations of individual pollutants at multiple monitoring sites across Hong Kong suggest that the average calculated daily values of pollutant concentrations were sufficient to capture day-to-day regional variations. As with most time-series studies, the investigators did not explore how spatial variation in daily average pollution levels might have affected exposure measurement error, although they did include some spatial analyses as part of their assessment of the role of socioeconomic status.

The relatively strong correlation between NO_2 and PM_{10} across monitoring sites (with Spearman correlations of 0.65–0.80; see Investigators' Report Table 7) suggests that these pollutants originate from some common source or sources, most likely road traffic, and sets the stage for potential confounding of the effects of each pollutant by the other. O_3 was only moderately correlated with PM_{10} and NO_2, decreasing the concern of confounding for that pollutant.

Pollutant-Specific Effects on Mortality

The investigators reported that short-term increases in the concentration of each of the air pollutants evaluated — PM_{10}, NO_2, SO_2, and O_3 — were associated with increased daily mortality due to all natural (nonaccidental) causes at lag 0–1 day (see Investigators' Report Table 8). Of all the pollutants evaluated, NO_2 showed the most consistent and robust effects on mortality. However, the scientific and public health significance of differences in the size of the pollutant effect estimates, and even attempts to identify a specific pollutant or pollutants whose effects were seemingly more robust than those of other pollutants, should not be overemphasized or overinterpreted. These differences may be due to differential errors in pollutant exposure estimation (discussed further in the Integrated Discussion in Part 5 of this volume) that together could have unpredictable impacts on the relative size and robustness of effect estimates. From what is known at this point about the toxicology of NO_2 (WHO 2006), there is little justification for attributing the effects on total mortality — and therefore the effects on cardiovascular mortality — to the direct toxic effects of NO_2.

Because most NO_2 in urban settings is derived from traffic-related pollution (HEI Panel on the Health Effects of Traffic-Related Air Pollution 2010), an effect of NO_2 is often interpreted to indicate an effect related to traffic. While that may be the case in the current study, it must be kept in mind that the results of time-series studies reflect relatively small, short-term, and often daily changes in pollutant concentrations that depend heavily on changes in meteorology, rather than changes in pollutant source emissions. We do not know how good daily average NO_2 concentrations (averaged across multiple sites, some or all of which may not be directly influenced by roadway emissions) are as surrogates for other traffic-related pollutants that have more pronounced concentration gradients around roadways than NO_2.

Whether short-term changes in the concentration of traffic-related pollutants can produce life-threatening effects in urban populations is not known, although this is strongly suspected (HEI Panel on the Health Effects of Traffic-Related Air Pollution 2010). It might be argued that ultrafine particles and other traffic-related pollutants are able to produce such effects. However, because their concentrations over time typically do not correlate with those of NO_2, it is difficult to see how they could be responsible for the NO_2 effects observed here. Results in two U.S. cities, Baltimore and Boston, suggest that ambient NO_2 concentrations are correlated with personal concentrations of ambient fine PM with an aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$) (Sarnat et al. 2000, 2005), so the effects of ambient NO_2 may then simply indicate the effects of $PM_{2.5}$. Whether the correlations in Baltimore and Boston that underlie this argument are similar in Hong Kong remains to be determined. It would be valuable in a future study to have information on $PM_{2.5}$, in addition to PM_{10} and NO_2, to gain insight into their inter-relations and the independent role of NO_2.

Sensitivity of Pollutant Effects to Other Factors

Meteorology The estimates of pollutant effects on mortality were sensitive to the specification of meteorology, with the effects of all the pollutants substantially attenuated by the inclusion of longer lags for humidity and temperature. The analyses of the sensitivity of the estimated pollutant effects to the inclusion of temperature terms for mean temperature over lag 1–2 days and (separately) lag 3–7 days were useful, though results that included the lag 1–2 and 3–7 terms simultaneously — which would have been of interest — were not reported. In general, coefficients were attenuated by adding longer-lag temperature terms, though all remained positive and many associations held. For example, the ER for mortality due to all natural causes for a 10-$\mu g/m^3$ increase in PM_{10} concentration (at lag 0–1 day) was reduced from 0.51% (95% CI, 0.23–0.80) to 0.31% (95% CI, 0.03–0.59) after adding a lag for temperature of 3–7 days (see Appendix M in the Investigators' Report).

This sensitivity to control for weather increases uncertainty as to whether the reported pollutant associations may still have been affected by changes in meteorology despite the investigators efforts to control for the effects of temperature. In the Discussion section of the Investigators' Report, the authors argue that "residual confounding due to a lack of additional adjustment for temperature at longer lags is unlikely, since the correlation between the residual from the model adjusted for temperature at lag 0 and the temperature itself at each 1–7 lag day is low." The Committee was not convinced by this argument; in our view, the fact that inclusion of longer-lag temperature terms changed pollution coefficients indicated that these correlations were large enough to cause confounding. The investigators also cited a high correlation between shorter- and longer-lag temperature terms as a reason for not using estimates from models that included longer-lag temperature terms. Parenthetically, the investigators argued that the more relevant correlations between the temperature lag terms would have been those evident after adjusting for other model terms, in particular for season. The Committee did not find this reasoning persuasive either; though including estimates from models incorporating longer-lag temperature terms might make interpretation of temperature coefficients problematic, there was no reason to think that it would bias pollution coefficients.

Controlling for Time Effects The positive associations reported in this study between individual pollutants and daily mortality and daily hospitalizations (discussed below) were largely unaffected by differences in the degree to which temporal trends in the data were controlled in the models (i.e., the degree of smoothing for time). This is reassuring. The degree of smoothing necessary to control for the effects of time-varying potential confounders while still being able to estimate any effects of exposure cannot be determined from the data in observational studies (HEI 2003). Exploring the sensitivity of the estimated pollutant effects to a range of alternative degrees of smoothing, as Wong and colleagues have done, currently provides the best assurance that estimates are not subject to residual confounding by smoothly changing covariates.

Sensitivity to Control for Other Pollutants No multipollutant model findings were presented in the report to allow assessment of the robustness of the pollutant effects to the inclusion of other pollutants in the models. While the interpretation of the pollutant effect estimates from multipollutant models is challenging when pollutants are highly correlated, it would nevertheless have been of interest to have at least assessed estimates from two-pollutant models for the robustness of the individual pollutant effects.

Pollutant Effects on Hospitalization and Their Consistency with Effects on Mortality

Wong and colleagues also included an assessment of the pollutant effects on hospitalizations over the same time period as the ER on mortality. They found that, based on the mean pollutant concentration at lag 0–1 day, short-term increases in the concentration of PM_{10}, NO_2, and SO_2 — but not O_3 — were associated with increased cardiovascular hospitalizations. All pollutants except SO_2 were also associated with increased respiratory hospitalizations (see Investigators' Report Table 9). Unlike with the mortality results, the investigators did not assess the robustness of the pollutant effects on hospitalizations after including longer humidity and temperature lags in their models. In light of the marked sensitivity of the mortality effects to more aggressive control for meteorology discussed earlier, it would have been valuable to know whether the effects on hospitalizations exhibited the same degree of sensitivity. Without this information, interpretation of the pollutant effects on hospitalization is more challenging.

The categorization differences in the mortality and hospital admissions databases (noted earlier) put some constraints on any assessment of the consistency between these two classes of health outcome with regard to the effects of air pollution. However, they were based on the same pollutant time-series data, and it is tempting to ask if the same pollutants are implicated in any effects on both mortality

and hospitalization, or if the same disease categories were affected by increases in pollution. For example, while chronic obstructive pulmonary disease (COPD) would likely be the underlying cause of death in someone with COPD who was dying of pneumonia, the discharge diagnosis of a patient with COPD who was hospitalized with pneumonia would likely be pneumonia.

Keeping in mind these caveats, there are nevertheless some interesting differences between the mortality and hospitalization results (see Investigators' Report Tables 8 and 9). O_3 was not associated with cardiovascular hospitalizations, but cardiovascular mortality was one of the only cause-of-death categories with which O_3 was associated. Furthermore, O_3 was associated with all categories of respiratory hospitalizations, but was not associated with respiratory death categories. For COPD deaths, NO_2 showed the largest and most statistically precise effect; all the pollutants considered were associated with COPD hospitalizations, though the largest effects were again seen for NO_2. One explanation for the effects of pollutants being larger on hospitalizations than on mortality may be the differences in disease categories between the causes of hospitalization and of mortality, as described earlier.

As is typically seen in time-series studies carried out in European and North American cities, effect estimates for all of the pollutants appeared larger for cardiovascular deaths than for total deaths due to natural causes (see Investigators' Report Table 8). The effect estimates for respiratory deaths were estimated with less precision than those for total natural or cardiovascular deaths because of the relatively small numbers of deaths. However, keeping that in mind, the respiratory death effect estimates were generally observed to be higher than the estimates for those causes, with the exception of O_3, where the effect estimate for respiratory deaths was small and consistent with no ER. The effect estimates for respiratory deaths in European and North American time-series studies are often, although not always, higher than those for any other category of deaths.

No pollutant was associated with increases in accidental mortality, for which there was a mean of only 4 deaths per day (Investigators' Report Table 3) and therefore limited power to detect effects. PM_{10}, NO_2, and SO_2, however, were each associated with increases in nonaccidental, non-cardiopulmonary mortality (see Table K.3 in Appendix K). No hospitalization diagnosis categories that might be considered "control" hospitalizations were evaluated. It was therefore not possible to determine whether associations with non-cardiopulmonary outcomes were present for hospitalizations as well as for mortality. See the Integrated Discussion (in Part 5 of this volume) for a discussion on the interpretation of associations between the pollutants and non-cardiopulmonary mortality.

Confounding Effects of Influenza

Wong and colleagues found that influenza activity—defined by their use of three different indices (indicating influenza intensity, influenza epidemic, and influenza predominance)—was associated with increased mortality and hospitalizations. Specifically, cardiovascular hospitalizations and respiratory hospitalizations (except for asthma, interestingly) increased during the periods of increased influenza activity. The investigators sought to address whether influenza activity either influenced (modified) the effects of the air pollutants or was a confounding factor (i.e., whether the apparent pollutant effects were in fact reflections of the effects of influenza).

One challenge in assessing the effects of influenza in a study of this sort is that there is no gold standard for measuring "influenza activity," and it is not clear how any of the three metrics compare with the metrics used in previous studies (Wong et al. 2002; Touloumi et al. 2005). Nonetheless, the Committee concurs with the investigators' conclusion that influenza activity did not materially confound the air pollutant associations with either mortality or hospitalizations, with the exception of hospitalizations for acute respiratory disease (Investigators' Report Table 19). The Committee also concurs with the investigators' caveats concerning the use of the change in estimate criterion to assess the presence of confounding in this study (Rothman et al. 2008). Application of an arbitrary criterion, such as that any adjustment for confounding must change the ER estimate by > 10%, in isolation ignores the precision of a given ER estimate. For subcategories of cause of death, changes in ERs estimated with low precision after control for confounding (see Investigators' Report Table 16) should not be relied on to indicate confounding, because such changes in estimates may be largely the result of stochastic variation.

The general absence of changes in the pollution effects on mortality after adjustment for influenza adds to the findings from studies in other parts of the world that also showed no confounding effects due to influenza (Braga et al. 2000; Touloumi et al. 2005), including the Bangkok PAPA study in this volume (see Part 3, Vichit-Vadakan et al.). The lack of confounding in the Hong Kong and Bangkok studies was, of course, not because influenza is not a predictor of mortality. Rather, it is because influenza was only weakly correlated with daily air pollutant concentrations,

which is not surprising given the lack of common determinants of influenza and pollution after accounting for meteorology. The apparent sensitivity to the effects of influenza on associations with hospitalizations for acute respiratory disease (ARD) is difficult to interpret. Influenza activity was not unexpectedly a strong predictor of ARD hospitalizations; the control for influenza may have dramatically reduced the variability in daily ARD hospitalizations such that with even weak correlations with air pollution, changes in pollutant effect estimates could have become unstable.

A particular focus of this study was the effect modification by influenza intensity and SDI of associations between health outcomes and air pollution. The statistical approach to modeling this — using analyses stratified by the putative modifier and estimating separate terms for each stratum — was sensible. However, the number of interactions explored was considerable, and some statistically significant associations are expected by chance in the presence of no effect modification. Thus, where statistically significant associations appear sporadically, interpretation should be extremely cautious. There was limited evidence that the mortality effects of the air pollutants were modified by SDI, most notably for NO_2 and SO_2 where there appears to be a concentration–response relationship. There was no evidence that the effects of the air pollutants on hospitalizations were modified by SDI.

As well as requiring caution because of multiple comparisons, estimates of interaction have special vulnerability to residual confounding and other biases. In particular, for time-varying modifiers, if either main effect (i.e., related to either pollutant or influenza) is inadequately modeled, the estimate of interaction may be confounded as well. If the influenza effect — or that of a factor correlated with influenza — is not adequately modeled, residual confounding by influenza could cause a spurious modification of pollution by influenza. Analyses of the sensitivity of the modification of the pollution effects by influenza to other model terms (especially the time smoothing and weather terms) might have been reassuring, but are not presented by the investigators. Measurement error can also have different effects in different groups (even for time-invariant putative modifiers, such as SDI), resulting in the biasing of the estimates of effect modification.

The Committee, therefore, finds little evidence that the pollutant effects were modified by either influenza or SDI in this study. Further, because of the concerns discussed earlier regarding multiple comparisons, residual confounding, and measurement error, the Committee does not put much weight on the few results that seem to suggest such modification of effect.

SUMMARY AND CONCLUSIONS

This study by Dr. Wong and colleagues, based on 7 years of data, is the most extensive analysis to date of the effects of short-term exposure to air pollution and health in Hong Kong. It also presents the first extensive analyses in a major Asian city of the extent to which influenza activity and socioeconomic status may modify the effects of short-term exposure to air pollution on daily mortality and morbidity. The methods employed by the investigators were generally sound, and the Committee concurs with the investigators' major conclusions that short-term increases in levels of several of the pollutants monitored were associated with increases in daily mortality and hospitalization for cardiovascular and respiratory disease when weather, influenza activity, and other time-varying factors were taken into account. The Committee also concurs that this study provides little evidence that either influenza activity or socioeconomic status modified the ER of short-term air pollution on the measured health outcomes.

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